

INFORMATION TO USERS

This material was produced from a microfilm copy of the original document. While the most advanced technological means to photograph and reproduce this document have been used, the quality is heavily dependent upon the quality of the original submitted.

The following explanation of techniques is provided to help you understand markings or patterns which may appear on this reproduction.

- 1. The sign or "target" for pages apparently lacking from the document photographed is "Missing Page(s)". If it was possible to obtain the missing page(s) or section, they are spliced into the film along with adjacent pages. This may have necessitated cutting thru an image and duplicating adjacent pages to insure you complete continuity.**
- 2. When an image on the film is obliterated with a large round black mark, it is an indication that the photographer suspected that the copy may have moved during exposure and thus cause a blurred image. You will find a good image of the page in the adjacent frame.**
- 3. When a map, drawing or chart, etc., was part of the material being photographed the photographer followed a definite method in "sectioning" the material. It is customary to begin photoing at the upper left hand corner of a large sheet and to continue photoing from left to right in equal sections with a small overlap. If necessary, sectioning is continued again — beginning below the first row and continuing on until complete.**
- 4. The majority of users indicate that the textual content is of greatest value, however, a somewhat higher quality reproduction could be made from "photographs" if essential to the understanding of the dissertation. Silver prints of "photographs" may be ordered at additional charge by writing the Order Department, giving the catalog number, title, author and specific pages you wish reproduced.**
- 5. PLEASE NOTE: Some pages may have indistinct print. Filmed as received.**

Xerox University Microfilms

300 North Zeeb Road
Ann Arbor, Michigan 48106

74-30,077

**BOONE, James Ronald, 1946-
METAL HYDRIDE REDUCTION OF
KETONES: STEREOCHEMISTRY
AND KINETICS.**

**Georgia Institute of Technology, Ph.D., 1974
Chemistry, organic**

Xerox University Microfilms, Ann Arbor, Michigan 48106

METAL HYDRIDE REDUCTION OF KETONES:
STEREOCHEMISTRY AND KINETICS

A THESIS

Presented to

The Faculty of the Graduate Division

by

James Ronald Boone

In Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy in the
School of Chemistry

Georgia Institute of Technology

August 1974

METAL HYDRIDE REDUCTION OF KETONES:
STEREOCHEMISTRY AND KINETICS

Approved:

EC. Ashby

E. C. Ashby, Chairman

Herbert O House

H. O. House

Erolin Grovenstein, Jr.

E. Grovenstein, Jr.

Date Approved by Chairman: *August 9, 1974*

ACKNOWLEDGMENTS

The author wishes to thank his advisor, Dr. E. C. Ashby, for his guidance throughout the course of this work. Dr. Ashby suggested these problems, and his constant interest and enthusiasm were instrumental in their successful completion. The author expresses his gratitude to Drs. E. Grovenstein, Jr. and H. O. House for their useful suggestions during the reading of the first draft of this thesis.

The author has held an instructorship, NDEA Fellowship, and PRF assistantship during the completion of this work for which he is grateful. A special acknowledgment and thanks are due Dr. W. M. Spicer for the opportunity to teach chemistry at the Georgia Institute of Technology and for advice and counseling given the author.

The author wishes to thank his wife, Rosemary, for her patience, encouragement, understanding, love, and help during these studies.

TABLE OF CONTENTS

	Page
ACKNOWLEDGMENTS	ii
LIST OF TABLES	v
LIST OF ILLUSTRATIONS	vii
SUMMARY	viii

PART I

STEREOCHEMISTRY OF METAL HYDRIDE
REDUCTION OF KETONES

Chapter

I.	INTRODUCTION	2
	Background Purpose	
II.	EXPERIMENTAL	10
	Materials Solvents Ketones Hydrides Reduction Procedure	
III.	RESULTS AND DISCUSSION	19
	Stereoselective Reductions of Model Ketones Reduction of 4- <u>tert</u> -Butylcyclohexanone Reduction of 2-Methylcyclohexanone Reduction of 3,3,5-Trimethylcyclohexanone Reduction of Norcamphor Reduction of Camphor General Considerations Concerning Alumino- hydrides as Reducing Agents Reductions with LiBH ₄ Reduction of Cyclopentanones Reduction of Ketones by Insoluble Hydrides The Selectivity of LiAl(OR) ₃ H as a Reducing Agent Solvation Effects	

TABLE OF CONTENTS (Continued)

Chapter	Page
III. (Continued)	
The Evaluation of Other Hydrides for Stereoselectivity Product Development Control and Recent Theories of Stereochemical Control Conclusions	
LITERATURE CITED	77
PART II	
KINETICS OF METAL HYDRIDE REDUCTION OF KETONES	
Chapter	
I. INTRODUCTION	82
Background Purpose	
II. EXPERIMENTAL	96
Materials Apparatus and Procedure Preparations Ultraviolet and Visible Spectra Product Analysis Kinetic Experiments	
III. RESULTS AND DISCUSSION	105
Kinetics of Reduction of MPK by Lithium Aluminum Hydride Kinetics of Reduction of MPK by Sodium Aluminum Hydride Kinetics of Reduction of MPK by Lithium Aluminum Deuteride Kinetics of Reduction of MPK by Aluminum Hydride Conclusions	
LITERATURE CITED	131
VITA	134

LIST OF TABLES

PART I

STEREOCHEMISTRY OF METAL HYDRIDE
REDUCTION OF KETONES

Table	Page
1. Reduction of Some Representative Ketones with a Series of Complex Aluminohydrides (MAlH_4) in THF	55
2. Percent <u>Cis</u> Alcohol from the Reaction of Complex Metal Hydrides with Cyclohexanones in THF	58
3. Reduction of Some Representative Ketones with LiBH_4 in THF	59
4. Reduction of Cyclopentanones with LiAlH_4 , $\text{Mg}(\text{AlH}_4)_2$, and ClMgAlH_4 in THF	60
5. Reduction of <u>4-tert-Butylcyclohexanone</u> , <u>3,3,5-Trimethylcyclohexanone</u> , and Camphor with Some Insoluble Complex Metal Hydrides	61
6. Reduction of <u>4-tert-Butylcyclohexanone</u> and <u>2-Methylcyclohexanone</u> with $\text{LiAl}(\text{O}^t\text{Bu})_3\text{H}$, $\text{LiAl}(\text{OCH}_3)_3\text{H}$, and LiAlH_4 at Varying Concentrations in THF	64
7. Reaction of <u>3,3,5-Trimethylcyclohexanone</u> with LiAlH_4 and NaAlH_4 at Varying Concentrations in THF	67
8. Reduction of <u>4-tert-Butylcyclohexanone</u> and <u>3,3,5-Trimethylcyclohexanone</u> with Lithium Triaryloxy Aluminohydrides in THF	69
9. Reduction of <u>3,3,5-Trimethylcyclohexanone</u> by LiAlH_4 in Diethyl Ether, THF, and DME, and by NaAlH_4 in THF and DME	70

LIST OF TABLES (Continued)

Table		Page
10.	Reduction of 3,3,5-Trimethylcyclohexanone in Diethyl Ether by LiAlH_4 at Varying THF:Li Ratios	71
11.	Reduction of 3,3,5-Trimethylcyclohexanone by LiAlH_4 in Diethyl Ether and Diethyl Ether-Benzene Mixtures at Varying TMED:Li Ratios	72
12.	Reduction of 3,3,5-Trimethylcyclohexanone by LiAlH_4 , NaAlH_4 , and KAlH_4 in the Presence of Crown Ethers	73
13.	Reduction of Some Representative Ketones with Some Soluble Metal Hydrides	74
14.	Relative Rate Constants for the Reaction of Selected Ketones with NaBH_4 in Isopropyl Alcohol	76

PART II

KINETICS OF METAL HYDRIDE REDUCTION OF KETONES

Table		Page
1.	Reaction of LiAlH_4 with Mesityl Phenyl Ketone in THF at 25.0°	126
2.	Reaction of LiAlH_4 with Mesityl Phenyl Ketone in THF at 25.0°	127
3.	Reaction of NaAlH_4 with Mesityl Phenyl Ketone in THF at 25.0°	128
4.	Reaction of LiAlD_4 with Mesityl Phenyl Ketone in THF at 25.0°	129
5.	Reaction of AlH_3 with Mesityl Phenyl Ketone in THF at 25.0°	130

LIST OF ILLUSTRATIONS

PART I

STEREOCHEMISTRY OF METAL HYDRIDE
REDUCTION OF KETONES

Figure		Page
1.	Hyperconjugation of the π Bond with the β C-C Bonds in Cyclohexanones	48
2.	Hyperconjugation of the π Bond with the β C-H Bonds in Cyclohexanones	50

PART II

KINETICS OF METAL HYDRIDE REDUCTION OF KETONES

Figure		Page
1.	Reaction of Mesityl Phenyl Ketone with Excess LiAlH_4	107
2.	Reaction of 5.2×10^{-5} M Mesityl Phenyl Ketone with Varying Concentrations of LiAlH_4	108
3.	Reaction of Mesityl Phenyl Ketone with Excess NaAlH_4	113

SUMMARY

PART I

STEREOCHEMISTRY OF METAL HYDRIDE
REDUCTION OF KETONES

The stereochemistry of reduction of selected ketones by a variety of simple and complex metal hydrides, both old and new, has been investigated under identical conditions of solvent, concentration, stoichiometry, temperature and reaction time for comparison purposes. The stereochemical results of these studies are discussed in terms of steric approach control, torsional strain, compression effect, and change in conformation of the ketone. The stereochemistry of reduction of complex aluminohydrides is shown to be dependent on the nature of the cation. Comparison of LiAlH_4 and LiBH_4 as reducing agents towards ketones shows LiBH_4 to be less sensitive to steric interactions. Reduction of 2-methylcyclohexanone with ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$ gave results best explained by assuming complexation of the carbonyl oxygen by magnesium followed by a change in the conformation of the ketone (methyl group equatorial to axial). Results obtained from reduction studies of substituted cyclopentanones and cis-2-methyl-4-tert-butylcyclohexanone do not suggest the presence of a compression effect in metal hydride reductions.

A study of the reduction of ketones by $\text{LiAl(OR)}_3\text{H}$ compounds shows the stereochemistry to be independent of concentration. The stereochemistry of reduction of ketones by LiAlH_4 and LiAlD_4 is similar.

PART II

KINETICS OF COMPLEX METAL HYDRIDE REDUCTIONS OF KETONES

Pseudo first order kinetic studies on the reaction of LiAlH_4 , NaAlH_4 and LiAlD_4 with mesityl phenyl ketone have been carried out in tetrahydrofuran at 25° . The reactions were carried out in excess hydride and found to be first order in hydride and first order in ketone. LiAlH_4 is about ten times more reactive than NaAlH_4 which indicates the importance of the cation in the mechanism of the reaction. A deuterium kinetic isotope study involving the reaction of LiAlH_4 and LiAlD_4 with mesityl phenyl ketone gave a value of $k_{\text{H}}/k_{\text{D}}$ of 1.27 which implicates the transfer of the hydride from aluminum to the carbonyl carbon in the rate determining step of the reaction. Aluminum hydride is about ten times less reactive than LiAlH_4 in the reduction of mesityl phenyl ketone.

PART I

STEREOCHEMISTRY OF METAL HYDRIDE
REDUCTION OF KETONES

CHAPTER I

INTRODUCTION

Background

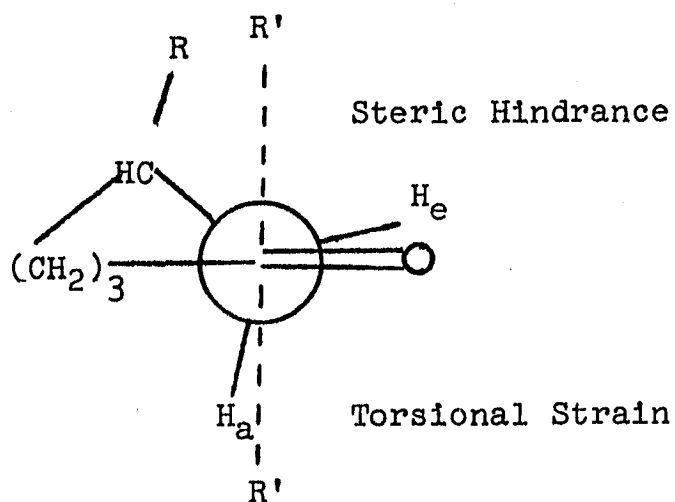
In recent years the area of stereoselective reduction of ketones by AlH_3 , LiAlH_4 , and their alkoxy derivatives has been investigated by many workers.^{1,2} Lithium aluminum hydride reduces 4-tert-butylcyclohexanone by predominantly attacking (90%) the molecule from the more hindered axial side to give^{3,4} the more stable equatorial alcohol. The more hindered ketone 3,3,5-trimethylcyclohexanone is attacked predominantly (55-75%)⁵ from the less hindered equatorial side to give the less stable axial alcohol. These results were first explained by Dauben who suggested the concept of, "product development and steric approach control".⁶ Dauben visualized the formation of an initial complex as the nucleophile approached the π bond of the carbonyl group followed by collapse of the complex to products. He further suggested that transfer of the hydride in the complex results in rehybridization of the carbonyl carbon atom from sp^2 to sp^3 . A late transition state in which hybridization is largely sp^3 allows the relative stabilities of the products to reflect themselves in the transition state. In the case of an unhindered ketone such as 4-tert-butylcyclohexanone, the

developing sp^3 hybridization is the controlling factor and hence "product development control" is observed. On the other hand, the C-3 axial methyl group of 3,3,5-trimethylcyclohexanone hinders the nucleophile in its axial approach and thus the ease of formation of this complex is decreased. This results in equatorial attack being favored and "steric approach control" governs the reduction. These and other results have been generalized^{6,7} to conclude that reduction of unhindered ketones is governed by "product development control" and reduction of hindered ketones is governed by "steric approach control". It is accepted that "product development control" would require a late transition state resembling the products while "steric approach control" would require an early transition state resembling the reactants.

In 1968 Cherest and Felkin⁸⁻¹¹ suggested that there should be no fundamental difference between the mechanisms of hydride reduction of hindered and unhindered cyclohexanones and the factors controlling stereochemical results of these reductions should be the same in each case. They assumed the transition state to be reactant like in all cases and introduced the concept of torsional strain to explain the large amount of axial attack by hydrides of 4-tert-butylcyclohexanone.

As shown below, equatorial attack on a cyclohexanone introduces torsional strain between the axial C-H bonds (H_a) at C-2 and C-6 and the forming C-H bond at C-1 which partially

eclipses them. Axial attack causes steric hindrance between the incoming hydride (R') and the axial substituents (R) at C-3 and C-5.



When R is a hydrogen as in 4-tert-butylcyclohexanone, torsional strain is greater than steric hindrance so the hydride prefers to attack axially. When R is a methyl as in 3,3,5-trimethylcyclohexanone, steric hindrance is increased such that equatorial attack is preferred.

Klein¹² has suggested that axial attack on 4-tert-butylcyclohexanone is preferred to equatorial attack because axial attack does not require the C-O bond to swing past the two equatorial C-H bonds at C-2 and C-6. This is torsional strain but is different from that proposed by Cherest and Felkin which involves the two axial C-H bonds at C-2 and C-6.

What Cherest and Felkin attributed to torsional effects of the axial C-2 and C-6 substituents, Richer¹³ attributed to steric hindrance. Since LiAlH_4 reduction of cis-2-methyl-4-tert-butylcyclohexanone² and 2,2-dimethyl-4-tert-butylcyclohexanone^{14,15} is reported to give the same amount of equatorial attack as reduction of 4-tert-butylcyclohexanone, steric hindrance by an axial C-2 methyl group to equatorial attack by LiAlH_4 appears to be minor. Equal rates of equatorial attack by lithium tri-tert-butoxyaluminumhydride $[\text{LiAl}(\text{O}^t\text{Bu})_3\text{H}]$ on 2,2-dimethyl-4-tert-butylcyclohexanone and 4-tert-butylcyclohexanone support such a conclusion.^{14,15} Thus, it appears that Cherest and Felkin's theory of stereoselective reductions being controlled by both steric hindrance (axial attack) and torsional strain (equatorial attack) is consistent with the facts and explains results not only with cyclic ketones but also acyclic ketones.

Recently Klein¹⁶ and others¹⁷ have presented new stereochemical control theories for metal hydride reduction of ketones based on orbital symmetry arguments and unequal distortion of the electron density about the carbonyl group. More is to be said about these theories in Chapter III.

The mechanism of hydride reduction of ketones is not well understood. While a considerable number of kinetic studies have been carried out with NaBH_4 ^{18,19,20} and BH_3 ^{21,22} little kinetic work has been reported for the reactions of simple and complex metal hydrides of aluminum with ketones.^{14,15,23}

Although it has been established that reduction of ketones by NaBH_4 in isopropyl alcohol is first order in each reactant, a variety of transition states are possible that will satisfy the kinetic data. Reaction of $\text{LiAl}(\text{OBu}^t)_3\text{H}$ with a series of substituted cyclohexanones has been reported to be first order in each reactant.¹⁴ A Hammett study²³ using substituted benzophenones with $\text{LiAl}(\text{OBu}^t)_3\text{H}$ and AlH_3 gave positive ρ values and was interpreted as indicating an accumulation of negative charge on the carbonyl carbon atom in the transition state. The data is insufficient however, to allow a more detailed description of the mechanism than that suggested by the kinetic data.

The importance of the cation in ketone reductions has been investigated for complex metal borohydrides. The borohydride ion was found to require a protic solvent or the presence of lithium or magnesium ions in order to be effective in the reduction of esters²⁴ and ketones.²⁵ The lithium ion may catalyze the reduction by polarizing the B-H bond or the C=O bond. On the other hand, NaAlH_4 ²⁶ and its alkoxy derivatives²⁷ are known to reduce ketones; therefore, the lithium ion is not necessary for the reduction of ketones by complex aluminohydrides. It has been suggested¹ that reduction of ketones by LiAlH_4 may involve a prior or synchronous association of the carbonyl oxygen atom with the lithium cation which assists the hydrogen transfer.

If complexation of the carbonyl group is rate deter-

mining, then reaction rates should reflect the rate of complexation of the ketone by the hydride. However, because of the large difference in the rate of reduction of a series of cyclohexanones with $\text{LiAl}(\text{OBu}^t)_3\text{H}$,¹⁵ it was concluded that complexation of the ketone by the hydride was not rate determining. The rate of complexation should be about equal for the series. It was pointed out, however, that the importance of complexation of the carbonyl group by the hydride on the stereochemistry of such reductions is not known.

Lithium trimethoxyaluminumhydride [$\text{LiAl}(\text{OCH}_3)_3\text{H}$] and $\text{LiAl}(\text{OBu}^t)_3\text{H}$ have been investigated as stereoselective reducing agents. $\text{LiAl}(\text{OCH}_3)_3\text{H}$ shows a much larger steric requirement than LiAlH_4 or $\text{LiAl}(\text{OBu}^t)_3\text{H}$. It has been suggested that the reason $\text{LiAl}(\text{OCH}_3)_3\text{H}$ behaves as if it is larger than $\text{LiAl}(\text{OBu}^t)_3\text{H}$ is because $\text{LiAl}(\text{OBu}^t)_3\text{H}$ disproportionates to lithium tert-butoxide and di-tert-butoxyalane.^{7,28} Later it was shown²⁹ that di-tert-butoxyalane and $\text{LiAl}(\text{OBu}^t)_3\text{H}$ give different stereochemical results with certain ketones, therefore, di-tert-butoxyalane is not the active reducing species in $\text{LiAl}(\text{OBu}^t)_3\text{H}$ solutions. It was also suggested that the greater stereoselectivity of $\text{LiAl}(\text{OCH}_3)_3\text{H}$ compared to $\text{LiAl}(\text{OBu}^t)_3\text{H}$ could be ascribed to the higher degree of association of $\text{LiAl}(\text{OCH}_3)_3\text{H}$ and hence its greater steric requirement.

Reduction of 3,3,5-trimethylcyclohexanone by LiAlH_4 in diethyl ether and tetrahydrofuran (THF) give different

results⁴ 55 and 75% equatorial attack respectively. Therefore, solvation of the LiAlH_4 appears to be important in determining the stereochemistry of reduction of ketones. Recently it was determined that LiAlH_4 has a much higher molar conductance in THF than diethyl ether.³⁰ This observation was used to suggest that LiAlH_4 in THF is more selective than in diethyl ether because LiAlH_4 is a solvent separated ion pair in THF while it is best described as a contact ion pair in diethyl ether.

Purpose

Unfortunately, the value of the literature for comparing one hydride reduction to another is often diminished significantly because of the wide variation in experimental conditions used. The purpose of this work was to evaluate complex aluminohydrides as stereoselective reducing agents toward model ketones under identical conditions with the hope that emerging patterns might appear. Reactant concentration, temperature, cation, solvent, stoichiometry, and order of addition of reactant were held constant for each study. For example, it was thought that if the nature of the cation was important it would be reflected in the stereochemical results provided that all the data was collected at the same temperature, solvent, concentration, etc. The effect of various solvents and complexation of the cation with crown ethers was also investigated. LiAlH_4 was also

compared to LiBH_4 and to a number of other simple and complex metal hydrides as reducing agents toward ketones.

CHAPTER II

EXPERIMENTAL

MaterialsSolvents

Fisher reagent grade anhydrous diethyl ether was distilled under nitrogen from LiAlH_4 prior to use.

Fisher reagent grade tetrahydrofuran (THF), benzene, and 1,2-dimethoxyethane (DME) was distilled under nitrogen from NaAlH_4 prior to use.

Fisher reagent grade N,N,N',N'-tetramethylethylenediamine (TMED) was distilled from and stored over Linde 4A Molecular Sieve.

Dibenzo-18-crown-6 and dicyclohexyl-18-crown-6 ethers were obtained from Drs. D. J. Cram and H. O. House, respectively and were used without further purification.

Ketones

2-Methylcyclohexanone (Eastman), norcamphor (Aldrich), camphor (Aldrich), 3,3,5-trimethylcyclohexanone (Chemical Samples), and 4-tert-butylcyclohexanone (Frinton) were purified by vacuum distillation or sublimation.

2-Methylcyclopentanone, 3-methylcyclopentanone and cis-3,4-dimethylcyclopentanone (Chemical Samples) were used without further purification except for drying with activated

Linde 4A Molecular Sieve.

Cis-2-methyl-4-tert-butylcyclohexanone was obtained from a preparation by J. P. Oliver, a coworker. It was 98% pure by gas chromatographic analysis.

Solutions of ketones were prepared by dissolving a known amount of ketone up to a known volume with solvent using syringes and flasks fitted with a 3-way stopcock which had been flamed out and cooled under nitrogen.

Hydrides

Lithium aluminum hydride, sodium aluminum hydride, lithium aluminum deuteride, and lithium borohydride were obtained from Alfa Inorganics. Solutions were prepared by distilling solvent onto the hydride and stirring the resulting slurry at least 24 hours. The slurry was filtered in the dry box through a fritted glass funnel. The clear and colorless solutions of LiAlH_4 , LiAlD_4 , and NaAlH_4 were standardized by aluminum analysis. The LiBH_4 was also clear and colorless and standardized by lithium analysis.

Tri-n-octyl-n-propylammonium aluminum hydride (NR_4AlH_4) was prepared by reported methods.³¹ Eastman tri-n-octyl-n-propylammonium bromide was dried at 50°C under vacuum overnight followed by distillation of THF onto the dry solid. The resulting yellow solution was standardized by bromide analysis. With a syringe, 0.427 moles of tri-n-octyl-n-propylammonium bromide was added to 0.413 moles of NaAlH_4 in THF and the resulting mixture was filtered in the

dry box. The clear yellow solution was standardized by aluminum analysis and gave an Al:H ratio of 1.00:3.83. A sodium analysis was 0.6% of the aluminum analysis.

Magnesium aluminum hydride and chloromagnesium aluminum hydride were prepared by previously reported methods.³² With a syringe 0.862 moles NaAlH_4 in THF was added to 0.435 moles of MgCl_2 (prepared by reacting magnesium metal with HgCl_2 in THF). The resulting white precipitate, a mixture of NaCl and $\text{Mg}(\text{AlH}_4)_2$, was collected and gave a Mg:Al:H ratio of 0.92:2.00:7.76. A sample of $\text{Mg}(\text{AlH}_4)_2$ was removed from the NaCl by Soxhlet extraction with THF. Similarly 0.523 moles of NaAlH_4 was added to 0.524 moles of MgCl_2 . The NaCl was removed by filtration and the resulting clear colorless THF solution of ClMgAlH_4 gave a Cl:Mg:Al:H ratio of 0.97:0.97:1.00:3.92.

Activated magnesium hydride was prepared from NaH and activated MgBr_2 as previously described.³³ A measured volume of the MgH_2 - NaBr slurry was removed with stirring and standardized by hydrogen analysis (gas evolution). The MgH_2 was not dried in order to avoid any loss in activity. The yield of MgH_2 was 93% as determined by amount of bromine remaining in solution after allowing the NaBr to settle which could only be there in the form of MgBr_2 .

Sodium aluminum hexahydride³⁴ (Na_3AlH_6) was prepared as previously described by reacting sodium, aluminum, and hydrogen at 2,000 psi and 160° in toluene. Analysis gave

the ratio Na:Al:H = 3.0:1.1:6.2. X-ray powder diffraction analysis showed only lines reported for Na_3AlH_6 .

The other hydrides used in this study (Li_2ZnH_4 ,³⁵ NaMgH_3 ,³⁵ KAlH_4 ,³⁵ NR_4MgH_3 ³⁶ (NR_4 = tri-n-octyl-n-propyl-ammonium ion), HBeCl ,³⁷ and AlH_3 ³⁷ were also obtained by previously reported methods.

Methanol and tert-butyl alcohol were distilled from magnesium and sodium, respectively. Phenol, 4-tert-butylphenol, and 4-chlorophenol were dried under vacuum at room temperature and stored over activated 4A molecular sieve in THF. The trialkoxy and triaryloxy derivatives of LiAlH_4 were prepared by slowly adding 3 moles of the alcohol or phenol in THF to 1 mole of LiAlH_4 in THF. The lithium trimethoxyaluminohydride was prepared at 0° and used within 24 hours. The analyses were as follows: lithium trimethoxyaluminohydride; Al:H = 1.00:0.99, lithium tri-tert-butoxyaluminohydride, Al:H = 1.00:1.00; lithium triphenoxyaluminohydride, Al:H = 1.00:0.98; lithium tri-4-chlorophenoxyaluminohydride, Al:H = 1.00:0.97; lithium tri-4-tert-butylphenoxyaluminohydride, Al:H = 1.00:0.97.

Magnesium analyses were carried out by EDTA titration of a hydrolyzed aliquot at pH 10 using Eriochrome Black T as an indicator (aluminum if present was marked with triethanolamine). Aluminum analyses were carried out by EDTA-zinc acetate back titration at pH 4 using dithizone as an indicator. Halide analyses were carried out by Volhard titration.

Hydride analyses were carried out by measuring the volume of H_2 evolved by an aliquot upon hydrolysis. Lithium and sodium analyses were carried out by flame photometry.

Reduction Procedure

A 50 ml Erlenmeyer flask with a magnetic stirring bar was flamed under nitrogen flush to remove residual water and oxygen. While still hot, it was fitted with a rubber septum and allowed to cool under nitrogen. The flask was kept under a slight positive N_2 pressure during the reaction. The homogeneous reactions were run at two ratios, $H^-/ketone = 6.0$ and $H^-/ketone = 1$. For the excess hydride reactions 6.0 ml of 0.50 M hydride in THF were added to the flask. The flask was cooled to $0^\circ C$ and 4.0 ml of 0.50 M ketone in THF were added. In the reactions with excess ketone, 2.0 ml of hydride solution were added to 8.0 ml of ketone at $0^\circ C$. The reactions were quenched after about 2 hours with distilled water or a saturated NH_4Cl solution. The internal standard was added and vpc analyses were carried out.

Samples of norcamphor and 3,3,5-trimethylcyclohexanone reacting with $LiBH_4$ were removed periodically and the absorbance of the $n \rightarrow \pi^*$ transition was measured. The reactions were complete within 2 hours. Reactions of camphor require a longer time before completion.

The heterogeneous reactions required adding the solid hydride to a tared flask in a dry box. With the weight of

hydride known the appropriate volumes of solvents and ketone solutions were added. The MgH_2 was not weighted but a measured volume of the slurry was added to the flask. The reactions were run with excess hydride and constant stirring.

The reactions of 3,3,5-trimethylcyclohexanone (III) with $LiAlH_4$ in diethyl ether and THF mixtures were run at $0^\circ C$ for 2 hours. A solution of THF in diethyl ether was prepared. To a known amount of a standard solution of $LiAlH_4$ in diethyl ether was added diethyl ether and the THF-diethyl ether mixture so that the resulting solution was 0.10 M in $LiAlH_4$ and the ratio THF:Li was known. The THF:Li ratio varied from 1.0 to 61. To this solution was added the appropriate amount of III (0.10 M in diethyl ether) so that the ratio H^- :ketone = 6.0.

Reaction of III with $LiAlH_4$ in diethyl ether in the presence of N,N,N',N'-tetramethylethylenediamine (TMED) were conducted similarly. Benzene was added to certain reactions to help increase the solubility of the complex when the complex was insoluble in diethyl ether.

The reactions of III with $LiAlH_4$ in diethyl ether, and $NaAlH_4$ and $KAlH_4$ in THF, in the presence of crown ethers were conducted at 0° for 2 hours. To a known weight of crown ethers was added solvent, then the hydride solution followed by ketone.

A twenty foot 5% carbowax 20 M on chromosorb G or fifteen foot 10% carbowax 20 M on diatoport S column was used

to separate the products of reaction of camphor (V) (150°C), norcamphor (IV) (125°C), 3,3,5-trimethylcyclohexanone (III) (125°C), and 4-tert-butylcyclohexanone (I) (150°C). Products from 2-methylcyclohexanone II and 2-methylcyclopentanone VII were separated on a fifteen foot 5% diglycerol column at 75°C .

Retention times varied slightly as different columns were used. For ketones I, II, III, IV, V, and VII the order of elution was always the same: the ketone first; the axial alcohol (I, II, III), exo alcohol (IV, V), and cis-alcohol (II, VII) second; and equatorial alcohol (I, II, III), endo alcohol (IV, V), and trans alcohol (II, VII) last. The cis-2-methyl-4-tert-butylcyclohexanone and its alcohols were separated on a 10 foot 10% carbowax 6M on chromosorb G at 180° . The order of elution was ketone, axial alcohol, equatorial alcohol.

Relative retention times are given for each ketone, cis or exo alcohol, trans or endo alcohol, and standard, respectively as follows: I, 1.00, 1.11, 1.32, 0.65; II, 1.00, 2.25, 2.95, 1.28; III, 1.00, 1.69, 1.44, 3.06; IV, 1.00, 1.46, 1.56, 0.83; V, 1.00, 1.39, 1.53, 0.62; VI, 1.00, 1.74, 2.33, (-); and VII, 1.00, 2.33, 3.30, (-). The internal standard used to measure yields for ketones I, II, IV, and V was III. Ethyl benzoate was used as the internal standard for III. No internal standard was used with VI and VII. Ratio of alcohols were also determined by nmr for VI and VII (also VIII and IX). The weight percent recovery of product for nmr

purpose was 80% or better.

The ratio of 2-methylcyclopentanol, 3-methylcyclopentanol, and cis-3,4-dimethylcyclopentanol were measured by nmr in DMSO-d₆. The assignments for the hydroxyl protons have been described by Battioni.³⁸

The hydroxyl proton nmr signal locations are cis-2-methylcyclopentanol, 4.10δ; trans-2-methylcyclopentanol, 4.38δ, cis-3-methylcyclopentanol, 4.35δ; trans-3-methylcyclopentanol, 4.26δ; cis, cis-3,4-dimethylcyclopentanol, 4.37δ; and trans, trans-3,4-dimethylcyclopentanol, 4.23δ. A possible problem with this method of analysis is that the hydroxyl hydrogen could possibly exchange with the deuteriums of the solvent (DMSO-d₆) under certain conditions. This problem did not appear significant in these cases because the hydroxyl hydrogen and the carbinol hydrogen integrated 1 to 1 and the nmr results did not change over a 24 hour period.

The reactions for cyclopentanones were carried out as described above. The reaction was quenched and dried with MgSO₄. The clear portion of the mixture was removed and put in another flask. The MgSO₄ and hydrolysates were washed several times with diethyl ether. The washings were combined and added to the original solutions. The solvent was then removed under reduced pressure and 0.5-1.0 ml of DMSO-d₆ added. TMS was the reference.

The ratio of alcohols from reducing cis-2-methyl-4-tert-butylcyclohexanone with Mg(AlH₄)₂ was also measured by

nmr. Results from nmr and glc analyses were in complete agreement. The hydroxyl proton nmr signals are located at 4.32 δ and 4.00 δ for the equatorial and axial alcohols, respectively, in DMSO-d₆ with TMS as the reference.

CHAPTER III

RESULTS AND DISCUSSION

A variety of complex metal hydrides were allowed to reduce several ketones which had the possibility of giving, on hydrolysis, isomeric alcohols. The ketones employed reflect different degrees of steric hindrance of approach to the carbonyl group. They also range from relatively flexible cyclic ketones, e.g., 2-methylcyclohexanone to rigid bicyclic ketones, e.g., norcamphor.

The homogeneous reductions were carried out at 0° in THF using two ratios of hydride to ketone (H^- :ketone = 6 and H^- :ketone = 1). The heterogeneous reductions were carried out at room temperature in the presence of excess hydride.

The ketones used in this study are 4-tert-butylcyclohexanone (I), 2-methylcyclohexanone (II), 3,3,5-trimethylcyclohexanone (III), norcamphor (IV), and camphor (V). The results of the reductions of the representative ketones with LiAlH_4 , NaAlH_4 , NR_4AlH_4 (NR_4 = tri-n-octyl-n-propylammonium ion), $\text{Mg}(\text{AlH}_4)_2$, and ClMgAlH_4 are given in Table 1. Most reactions were carried out under identical conditions. However, the $\text{Mg}(\text{AlH}_4)_2$ and ClMgAlH_4 were examined under different conditions due to their limited solubilities.

For this work the expression "more selective" will be

used to imply that a particular hydride gives a ratio of alcohol products further from a 1:1 ratio than does another hydride to which it is being compared.

Stereoselective Reductions of Model Ketones

Reduction of 4-tert-Butylcyclohexanone (I).

All the hydrides in Table 1 behave similarly towards I. A trend may be suggested with LiAlH_4 , NaAlH_4 , and NR_4AlH_4 . Although the results are reproducible, the accuracy of gas chromatographic analysis may cause doubts about the reality of the absolute figures. The 10% equatorial attack for LiAlH_4 gives a 1.0:9.0 ratio of products while 15% equatorial attack for NR_4AlH_4 gives 1.0:5.7 ratio of products and such a change in ratio should be accurately measurable by gas chromatography.

In the case of I steric hindrance and torsional strain favor different directions of attack. Torsional strain appears to be the dominating factor from the results of Table I, that is the hydrides give predominantly axial attack. Why LiAlH_4 and ClMgAlH_4 might experience torsional strain more than other hydrides is not readily apparent. The ratio of hydride to ketone seems to be of little importance with all the hydrides studied.

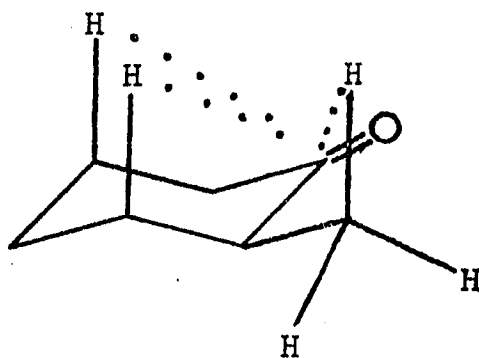
4-tert-Butylcyclohexanone should be a good model for the chair of cyclohexanone. The tert-butyl group is locked in an equatorial position and is removed from the reaction

center. Its induction, steric and field effect on the reaction center should be minimal. Therefore, the data in Table 1 should represent accurately the ratio of axial and equatorial attack on the cyclohexanone chair conformation.

Reduction of 2-methylcyclohexanone (II).

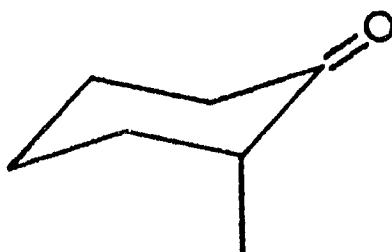
The hydrides in Table 1 are less similar in their selectivity towards II. Magnesium aluminum hydride and ClMgAlH_4 give 12-24% more apparent equatorial attack than LiAlH_4 . The other hydrides are similar to LiAlH_4 and give about 25% apparent equatorial attack.

All the hydrides give more equatorial attack on II than I, if the reactive conformation is considered to be IIe .



It has been suggested³⁹ that the hydrogen atoms of the methyl group introduce a third, 1,3-diaxial interaction with respect to the incoming nucleophile. This effect will, of course, retard axial attack. Reaction of II through the flexible form (the various boat and twist boat conformations) has also

been suggested⁴⁰ to explain the increase in equatorial attack on II over I. This increase in apparent equatorial attack has also been attributed^{6,41} to reaction of the chair conformation with the methyl group axial (IIa).



IIa

Axial attack on this conformation would give the cis alcohol accounting for the increase in apparent equatorial attack on II over I. 2-Methylcyclohexanone is reported⁴² to exist in such a conformation to the extent of approximately 5% at ambient temperature. It has been reported² that LiAlH_4 gives 91% axial attack on cis-2-methyl-4-tert-butylcyclohexanone. This result shows that the introduction of an equatorial 2-methyl group on I has not increased steric hindrance to axial attack since 4-tert-butylcyclohexanone gives 90% axial attack with LiAlH_4 . Thus, the suggestion that reaction of II partly via conformation IIa is the reason for an increase in apparent equatorial attack on II over I is supported. Reaction through the flexible form of II is less likely since it is present to a much smaller extent in solution than the chair conformation IIa. Significant reaction of II through more than one conform-

ation may make it a less attractive ketone for evaluation of hydrides as stereoselective reducing agents.

Magnesium aluminum hydride and ClMgAlH_4 give considerably more equatorial attack on II than LiAlH_4 while their results with I were similar to LiAlH_4 . This result is of considerable interest because it is believed that a satisfactory explanation might lead to a new insight into stereochemical control or mechanism of complex metal hydride reduction of ketones. An explanation based on steric hindrance was considered first. If ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$ have a larger steric requirement than LiAlH_4 , then they would possibly attack conformation IIe less from the axial side due to an increase steric hindrance introduced by the quasi-axial hydrogen of the methyl group. Such an explanation based on steric hindrance should also be consistent with observed stereochemical results for reduction of other ketones by LiAlH_4 , ClMgAlH_4 , and $\text{Mg}(\text{AlH}_4)_2$ and not conveniently invoked to explain the results with II. Magnesium aluminum hydride and ClMgAlH_4 give more axial attack on 3,3,5-trimethylcyclohexanone (III) and more exo attack on camphor (V), thus, they have a smaller steric requirement than LiAlH_4 in these two cases. Because results with II (IIe), III, and V when explained by steric hindrance do not consistently require ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$ to have a larger or smaller steric requirement than LiAlH_4 , another explanation was sought.

It was next considered that possibly more of conform-

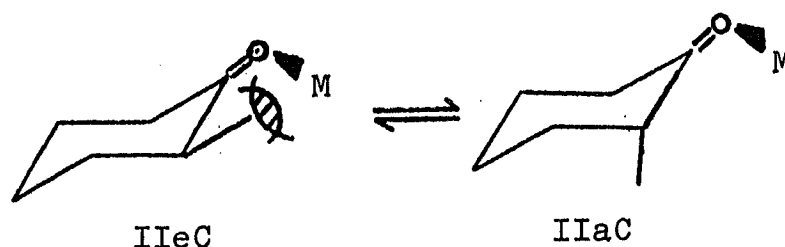
ation IIa is involved in the reaction when II is reduced by ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$ than LiAlH_4 . Such an explanation may be made by assuming that cation, M^+ , of MAlH_4 associates with the carbonyl oxygen during the reduction step. If the cation complexes the carbonyl oxygen prior to or concurrent to reduction, then the MgCl^+ or MgAlH_4^+ being larger than Li^+ would interact more with the methyl group of IIe and force more of the reaction to proceed through the chair conformation IIa. Such a conformation produces less interaction between the cation as it complexes the carbonyl oxygen atom and the methyl group.

Reduction of cis-2-methyl-4-tert-butylcyclohexanone (VI) by LiAlH_4 , ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$ was carried out⁴³ to investigate the possibility that cation complexation of the carbonyl oxygen satisfactorily explains the reduction data obtained for II. In the case of VI the methyl group is fixed in an equatorial position and since a change in conformation cannot easily occur, the stereochemical outcome should be nearly the same with all three hydrides as in the case of I. Results are given in Table 2.

Table 2 shows the extent of apparent equatorial attack on I, II, and VI. The results show the order of apparent equatorial attack on II (IIe) to be $\text{LiAlH}_4 < \text{ClMgAlH}_4 < \text{Mg}(\text{AlH}_4)_2$. The hydrides show less variation in the amount of equatorial attack on I and VI than II. Each hydride gives about twice the amount of equatorial attack on VI as I. The

results of this study show the steric requirement of each hydride to be nearly the same towards VI. The conclusion is that more of conformation IIa is involved in the reduction of II by $\text{Mg}(\text{AlH}_4)_2$ and ClMgAlH_4 than by LiAlH_4 . Although the hydrides give more equatorial attack on VI than I, the important consideration is that the amount of equatorial attack is about the same for each hydride and is too small to explain the amount of apparent equatorial attack on II if only conformation IIe is considered to be the reactive conformation.

It has been shown that lithium and magnesium salts or protic solvents catalyze^{24,25} borohydride reduction of ketones and esters. A mechanism suggested¹ for ketone reduction by LiAlH_4 involves prior or concurrent association of the carbonyl oxygen with Li^+ as the hydride is transferred. Such a mechanism is supported by these results. If complexation of the carbonyl group occurs during reduction, then the concentration of IIaC (and its transition state corresponding to axial attack) should increase relative to IIa since the energy difference between IIaC and IIeC is less than between IIa and IIe.



Therefore, it is not surprising that more reaction proceeds through IIa (IIaC) with bulkier complexing agents such as $-\text{MgCl}^+$ and $-\text{MgAlH}_4^+$, than with a smaller complexing agent such as Li^+ . From this result it is concluded that complexation of the carbonyl oxygen by the cation may indeed be a mechanistic pathway for these reductions. The results indicate that magnesium is involved in complexation, but not necessarily lithium; however, lithium would be very suspect. It has previously been shown that a ketone will associate with the lithium cation in tetrahydrofuran solution.³⁰

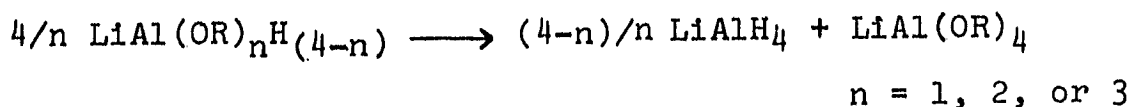
Each hydride in Table 2 gives twice the amount of equatorial attack on VI as I. Reduction of I, II, and VI by LiAlH_4 gives 10, 24, and 19% equatorial attack, respectively. If both conformations IIa (5%) and IIe (95%) have the same rate of reaction, then 19% equatorial attack on IIe by LiAlH_4 (since VI give 19% equatorial attack) plus a large amount of axial attack on IIa (present in 5%) produce approximately 24% apparent equatorial attack on II which is experimentally observed.

Results with VI indicate that the equatorial C-2 methyl group does hinder axial attack. This is surprising since from models it appears that the π cloud of the carbonyl group is hindered more by the C-3 and C-5 hydrogens than the quasi axial hydrogen of the methyl group. Although it might appear that hindrance by the C-2 methyl group to axial attack should be minor, in actuality the effect is significant resulting in

twice the amount of equatorial attack on VI as compared to I. The results can be explained by assuming that the C-2 methyl (1) blocks the axial approach of the aluminohydride ion from a direction perpendicular to the plane of the carbonyl group; (2) blocks the hydride from moving into an axial position after complexing the oxygen atom; or (3) causes steric strain between the cation as it complexes the oxygen atom and part of the reduction occurs via the flexible form. More work needs to be done in order to determine exactly why a decreased amount of axial attack is experienced on VI as compared to I. Regardless of the reasons it appears that both reaction of II via conformation IIa and some type of hindrance to axial attack by the methyl groups account for II giving an increase in equatorial attack over I.

Chloromagnesium aluminum hydride exhibits a change in selectivity when the ratio of hydride to II is varied but $\text{Mg}(\text{AlH}_4)_2$ does not show such a change. Results with II using the other hydrides in Table 1 show that selectivity is insensitive to ratio of reactants. Since $\text{Mg}(\text{AlH}_4)_2$ is only slightly soluble in THF, its reactions reported in Table 1 are probably only occurring in solution at one ratio (H^- : ketone ≤ 1 , i.e., excess ketone) even though the measured ratios are different. Since ClMgAlH_4 is soluble in THF, the results do indeed reflect reaction at two different ratios (H^- :ketone = 1 and 6). A change in stereochemistry for ClMgAlH_4 with ratio of reactants occurs not only for II but

also for III, IV, and V (Table 1). The effect of ratio of reactants on stereochemistry is negligible for LiAlH_4 and ketones I-V except for maybe III (Tables 1 and 6). Eliel has interpreted^{5,7} such results as indicating that LiAlH_4 is the reducing agent at all ratios because the following disproportionation reactions are very rapid.



If any alkoxy intermediates were reacting one would expect the steric requirement of the intermediate to be greater than LiAlH_4 and hence attack on the ketone from the least hindered side should increase. However, when excess III, IV and V ($\text{H}^-:\text{ketone} = 1$) are allowed to react with ClMgAlH_4 the results show increased attack from the more hindered side of the ketone than when excess hydride is used. Since dependence of the selectivity of ClMgAlH_4 on reactant ratio is opposite to what may have been expected for several ketones, a satisfactory explanation is not offered at this time.

Reduction of 3,3,5-Trimethylcyclohexanone (III).

Ketone III introduces a methyl group in the C-3 axial position which severely hinders axial attack on the cyclohexanone. The largest difference in the selectivity of the hydrides occurs with III (Table 1). Equatorial attack predominates for all hydrides and ratio of reactants (55-80%).

Steric hindrance is experienced more by LiAlH_4 than the other hydrides and results in the largest amount of equatorial attack (80%). The order of selectivity is $\text{LiAlH}_4 > \text{ClMg}(\text{AlH}_4)_2 > \text{Mg}(\text{AlH}_4)_2 \approx \text{NaAlH}_4 > \text{NR}_4\text{AlH}_4$.

Reduction of Norcamphor (IV).

Reductions of IV show a similar trend in selectivities of the hydrides as III: $\text{LiAlH}_4 \approx \text{ClMgAlH}_4 > \text{MgAlH}_4 > \text{NaAlH}_4 > \text{NR}_4\text{AlH}_4$. Steric hindrance and torsional strain favor opposite sides of attack in I, II, III, and V but not in IV where both favor exo attack. Torsional strain occurs between the $\text{C}_1\text{-C}_6$ bond and a hydride attacking endo. Although reductions of I and II are governed largely by torsional strain and III and V by steric hindrance, it is not so easy to decide what governs the reduction of IV. It is likely that both torsional strain and steric hindrance are important in the reduction of IV. Lithium aluminum hydride shows a similar degree of selectivity for IV and V (91% of the less stable isomer). If steric hindrance was the only important factor controlling the selectivity of a hydride towards IV as probably it is in V, then the other hydrides should show the same degree of selectivity for IV as they do V, just as LiAlH_4 does; however, this is not the case, thus factors other than steric hindrance must be important. Since I gives similar results with each hydride and torsional strain is believed to be the governing factor in the stereochemistry of reduction, it may be expected that each hydride would give about the same results with IV if

torsional strain was the only important factor controlling stereochemistry but neither is this the case. The large amount of exo attack on IV by all the hydrides can probably be best attributed to the fact that it is favored by both steric hindrance and torsional strain. The 18% spread in the selectivity of the hydrides may be attributed to how they experience the steric hindrance, thus they follow a trend similar to III.

Reduction of Camphor (V).

The hydrides LiAlH_4 , NaAlH_4 and NR_4AlH_4 are similar in their selectivity towards V; they give 87-91% endo attack. The syn C-7 methyl group severely blocks exo attack and the results are as expected. The hydrides ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$ give less endo attack (81 and 74%, respectively) than the other hydrides. This is unexpected since they appear to experience steric hindrance more than NaAlH_4 and NR_4AlH_4 with III and IV. If torsional strain is used to explain why ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$ give more exo attack on V than the other hydrides, then it is difficult to explain why they give more equatorial attack on III than NaAlH_4 and NR_4AlH_4 . Perhaps forces other than steric hindrance and torsional strain influence the stereochemical outcome of reductions of ketones.

General Considerations Concerning Aluminohydrides as Reducing Agents

The stereoselectivity can be seen from Table 1 to have some dependence upon the cation present. If the hydrides

containing magnesium are not considered, the smaller the cation (greater charge density) the more selective the hydride is towards I, III, and IV. Results with ketones II and V are too similar to allow any conclusions. It does appear that LiAlH_4 is the most selective hydride whether the stereochemistry is controlled by steric hindrance or torsional strain. This means that LiAlH_4 experiences torsional strain or steric hindrance more than the other hydrides, depending on the nature of the ketone.

The difference in selectivities may be due to two possible factors: (1) the cation participates directly in the step in which the stereochemistry is determined, or (2) the cation alters the reducing species in solution. Probably the most apparent mechanism by which the lithium ion may participate directly in the reaction would be for it to complex the ketone during reduction.¹ Brown has shown that the lithium ion catalyzes the reduction of ketones by the borohydride ion in aprotic solvents because LiBH_4 reduces acetone in aprotic solvents and NaBH_4 does not.²⁴ The lithium ion may enter into catalysis by either polarizing the carbonyl bond or the B-H bond.²⁴ If complexation of the carbonyl oxygen by the cation were to occur, the resulting influence on the stereochemistry is not readily apparent for all ketones even though its possible importance in the reduction of II was discussed. Since NaAlH_4 and NR_4AlH_4 will reduce ketones, it is not necessary for the reaction of the aluminohydride

ion to require the presence of the lithium cation. Since the reduction of V by NR_4AlH_4 is slower than by LiAlH_4 (Table 1), the lithium ion must catalyze the reaction in some manner. Since the lithium cation will associate with ketones in tetrahydrofuran,³⁰ it is not only possible, but probable that the lithium cation polarizes the carbonyl group increasing the rate of reaction.

It should not be overlooked that solvation of the cation may alter the reducing species. Reduction of III by LiAlH_4 in diethyl ether gives⁵ only 55% equatorial attack compared to 75% in THF ⁵ as solvent. This difference may be attributed to solvation effects, probably that of the cation. Solvation of MAlH_4 may vary with M, thus the stereochemistry may depend on M. Increasing solvation of M may increase the steric requirement of the hydride. The presence of a solvated cation in the transition state may require more order in the transition state for hydride transfer, thus a greater selectivity.

The magnesium cation is about the same size⁴⁴ as the lithium cation but carries a +2 charge instead of +1. In light of the above discussion $\text{Mg}(\text{AlH}_4)_2$ and ClMgAlH_4 may be expected to be more selective than LiAlH_4 towards III, IV and I because the magnesium cation would have a larger charge density than the lithium cation. This is not observed. It probably is unfair to try to make such comparison between $\text{Mg}(\text{AlH}_4)_2$ and ClMgAlH_4 , and LiAlH_4 because the nature of the

species in solution could be quite different.

Reductions with LiBH_4 .

Ketones I-V were reduced with LiBH_4 under identical conditions as with LiAlH_4 . The results are tabulated in Table 3. Reductions with LiBH_4 were slower than with LiAlH_4 . Reactions with III, IV, and V were followed spectrophotometrically to assure completion of reaction before quenching since considerable reduction was found to occur upon quenching.

Lithium borohydride gives results similar to LiAlH_4 for I and II where torsional strain is believed to be the controlling factor in determining the direction of attack. When the reduction is controlled by steric hindrance, III, IV, and V, LiBH_4 gives more attack than LiAlH_4 from the more hindered side. This is consistent with the borohydride ion being smaller⁴⁵ than the aluminohydride ion or that LiBH_4 is less solvated³⁰ than LiAlH_4 in THF, thus having a smaller steric requirement. When the ratio of H^- :ketone = 1, LiBH_4 is more selective for the ketones III, IV, and V and less selective for ketone II than when excess LiBH_4 was used. This is consistent with more of the reduction occurring via alkoxy intermediates at low hydride:ketone ratios.²⁰

Reduction of Cyclopentanones.

In order to compare the reduction of cyclopentanones to alkylation results using CH_3MgBr and $\text{Al}(\text{CH}_3)_3$,⁴⁶ 2-methylcyclopentanone (VII), 3-methylcyclopentanone (VIII), and 3,4-dimethylcyclopentanone (IX), were reduced with LiAlH_4 .

Results are tabulated in Table 4.

The preferred conformation of cyclopentanone, the half-chair model, has a C_2 axis of symmetry⁴⁷ which allows equal attack from either side. Substituents distort the symmetry causing one side to be attacked by hydride more easily than the other. Since VII is attacked 84% cis by $LiAlH_4$ to the methyl group, any steric hindrance from the C-2 methyl group seems to be minor. The methyl group is probably in a quasi-equatorial position and offers less steric hindrance than torsional strain by the quasi-axial hydrogen at C-2 on the other side of the ring.² Common methylating reagents [$Al(CH_3)_3$, CH_3MgBr] slightly hindered by the methyl group and give about 60% trans attack.⁴⁶

The ketone VIII is attacked 71-73% trans by $LiAlH_4$. This may at first glance be ascribed to steric hindrance of the C-3 methyl group blocking cis attack since the introduction of an axial C-3 methyl group on a cyclohexanone ring results in a large decrease in axial attack, from 90% to 20% (ketones I and III). This latter observation may clearly be ascribed to steric hindrance. However, it must be remembered that the cyclohexanone chair conformation does not allow equal attack on both sides while the half chair conformation of cyclopentanone does. Therefore, the C-3 methyl group of VIII only changes the preferred direction of attack from 50% to 72%. This is less than for the C-2 methyl group of VII (50% to 84%) whose stereochemistry of reduction is not con-

trolled by steric hindrance, but probably by torsional strain. Several methylating reagents, which usually have larger steric requirements than hydrides, give⁴⁶ only 60% trans attack on VIII. It is also reported that VIII and 3-tert-butylcyclopentanone are attacked the same amount trans (60%) by LiAlH_4 ³⁸ in diethyl ether. These results indicate that torsional strain or factors other than steric hindrance control the stereochemistry of reduction and alkylation of VIII. The C-3 methyl group is probably in a quasi-equatorial position and offers little steric hindrance to cis attack.

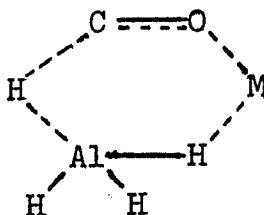
The vicinal methyl groups of IX probably twist in a manner to avoid eclipsing each other. One takes a quasi-axial position and the other a quasi-equatorial position. The quasi-axial methyl group can hinder cis attack on the carbonyl group, thus LiAlH_4 attacks IX 90% from the trans side. Methylating reagents also give⁴⁶ about 90% trans attack.

The large amount of apparent equatorial attack on II by ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$ was explained by the magnesium ion complexing the carbonyl oxygen and sterically interacting with the equatorial C-2 methyl group and forcing it into an axial position. This steric interaction is very similar to the "compression effect" used⁴⁶ to explain alkylation of cyclohexanones in benzene with $\text{Al}(\text{CH}_3)_3$. The "compression effect" is compression of the complexed carbonyl group against unequal substituents above or below the plane of the carbonyl group. The "compression effect" favors attack from the side

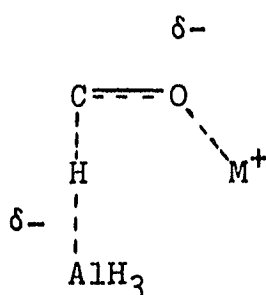
of the carbonyl group which will relieve the compression strain. The "compression effect" as described for alkylations does not seem to be operating in the cases considered here. If it was, the amount of axial attack on VI by LiAlH_4 , ClMgAlH_4 , and $\text{Mg}(\text{AlH}_4)_2$ should be greater than on I, whereas the opposite is observed.

To investigate the "compression effect" further, VII was reduced using ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$. It has been pointed out⁴⁶ that VII is a good model to test for the "compression effect". Results shown in Table 4 for the reduction of VII by ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$ is opposite to that expected for the "compression effect", that is they gave more trans attack than LiAlH_4 , therefore it is concluded that the "compression effect" is minor or inoperative in the reduction of ketones VI and VII by complex metal hydrides.

It appears that if ClMg^+ or AlH_4Mg^+ complexes the carbonyl group of VII it pushes the methyl group from its quasi-equatorial position which increases steric hindrance to cis attack. It is also possible that the methyl group prevents the alumino hydride ion, via a six center transition state, from swinging around to attack cis as the magnesium ion complex the carbonyl oxygen.



Reduction of VIII and IX by ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$ give results which are very similar to LiAlH_4 . Chloromagnesium aluminum hydride and $\text{Mg}(\text{AlH}_4)_2$ also give results with I, III, and IV which are similar to LiAlH_4 and NaAlH_4 . However, they give different results with II, V, and VII, where each ketone has a C-2 methyl group. A mechanism that would allow possible explanations for these results would involve the carbonyl-oxygen associating with the cation. Steric interaction between the substituent at C-2 and the complexing cation could alter the stereochemistry depending on the size of the complexing



agent and how strongly it complexes the oxygen atom.

Reduction of Ketones by Insoluble Hydrides

The crystal lattice network of an insoluble hydride should present a large steric requirement to a ketone, and thus should provide a high degree of selectivity. Several insoluble hydrides were investigated in order to test this concept. The results are tabulated in Table 5.

The most reactive hydride based on percentage of re-

covered I is Li_2ZnH_4 and the least reactive is NR_4MgH_3 . The amount of equatorial attack on I varied from 10-65%. Although MgH_2 and Na_3AlH_6 give more equatorial attack on I than LiAlH_4 , they give less equatorial and endo attack on III and V, respectively, than LiAlH_4 . Equilibration during reduction was shown to be important for MgH_2 . The reaction of III and a mixture of 3,3,5-trimethylcyclohexanols (75% trans) with MgH_2 gave a mixture of alcohols which was 20% trans with only 12% reduction of the ketone. Equilibration could be occurring similarly to Meerwein-Pondorff equilibration through Mg(OR)_2 as an intermediate. The reaction of III and a mixture of its alcohols (70% trans) with Na_3AlH_6 showed little or no equilibration. The recovered ketone, at least for Na_3AlH_6 , may not be attributed to enolate formation. Reaction samples to which LiAlH_4 was added before quenching gave about 1% recovered ketone, indicating that the ketone was unreacted and not enolized. The insoluble hydrides are capable of reducing ketones, but have no advantage over more common reducing agents.

The Selectivity of $\text{LiAl(OR)}_3\text{H}$ as a Reducing Agent

It was reported that the stereoselectivity of $\text{LiAl(OCH}_3)_3\text{H}$ towards II in THF depends on the concentration of the hydride in the reaction mixture.²⁹ The increased steric requirement of $\text{LiAl(OCH}_3)_3\text{H}$ over $\text{LiAl(OBu}^t)_3\text{H}$ was explained by the greater association of $\text{LiAl(OCH}_3)_3\text{H}$ compared to $\text{LiAl(OBu}^t)_3\text{H}$ in THF. It was felt that these results should

be checked because: (1) the monomer of $\text{LiAl}(\text{OBu}^t)_3\text{H}$ is approximately as large as the dimer or trimer of $\text{LiAl}(\text{OCH}_3)_3\text{H}$ (2) the previous results were obtained with only one ketone, II, which may have been a poor choice because the stereoselectivity seems to depend on which conformation reacts; and (3) only one out of four different concentrations showed a change in selectivity. The ketones I and II were examined over a 100 fold change in concentration of hydride, using LiAlH_4 , $\text{LiAl}(\text{OCH}_3)_3\text{H}$, and $\text{LiAl}(\text{OBu}^t)_3\text{H}$. The results are given in Table 6. These data show that there is no change in selectivity with concentration of hydride. This suggests that reductions with $\text{LiAl}(\text{OCH}_3)_3\text{H}$ occur by the same species at all concentrations or that the associated species have no greater steric requirement than the monomer.

These results leave us with no explanation for the difference in the selectivities of $\text{LiAl}(\text{OCH}_3)_3\text{H}$ and $\text{LiAl}(\text{OBu}^t)_3\text{H}$. Reaction of $\text{LiAl}(\text{OBu}^t)_3\text{H}$ via $\text{Al}(\text{OBu}^t)_2\text{H}$ as an intermediate²⁸ does not seem likely since it has been shown that $\text{LiAl}(\text{OBu}^t)_3\text{H}$ and $\text{Al}(\text{OBu}^t)_2\text{H}$ have different stereoselectivities²⁹ towards certain ketones. Reaction of $\text{LiAl}(\text{OBu}^t)_3\text{H}$ via LiAlH_4 from disproportionation does not seem likely either since LiAlH_4 will react with certain substrates that $\text{LiAl}(\text{OBu}^t)_3\text{H}$ will not.⁴⁸ The equivalent molar conductance³⁰ of $\text{LiAl}(\text{OCH}_3)_3\text{H}$ (2.32 mhos/cm² at 0.1 M) is much greater in THF than that of $\text{LiAl}(\text{OBu}^t)_3\text{H}$ (0.0124 mhos/cm² at 0.1 M) indicating that the former is more solvated. Less solvation of $\text{LiAl}(\text{OBu}^t)_3\text{H}$ may possibly allow

less steric strain or a different mechanism altogether for reduction of ketones than $\text{LiAl}(\text{OCH}_3)_3\text{H}$.

The stereoselectivity of LiAlH_4 towards I is essentially independent of concentration. However, results with II indicate that there may be some dependence on concentration. When III is allowed to react with LiAlH_4 and NaAlH_4 at varying concentrations, selectivity of hydride shows a dependence on concentration (Table 7).

Both LiAlH_4 and NaAlH_4 are more selective towards III at lower concentrations. Both LiAlH_4 and NaAlH_4 have been shown to be more associated at higher concentrations.³⁰ It may be thought that the less associated species would have less steric requirement and would be less selective. This is not observed. The lower concentrations give more equatorial attack on III. The nature of LiAlH_4 and NaAlH_4 in THF changes considerably with concentration. These results may be due to a change in the reducing species other than association, for example, solvation.³⁰ The results concerning NaAlH_4 in THF are similar to those of LiAlH_4 in diethyl ether. Possibly the solvation of NaAlH_4 in THF is similar to that of LiAlH_4 in diethyl ether and they give similar results with III.

Because the selectivity of $\text{LiAl}(\text{OCH}_3)_3\text{H}$ showed no dependence on concentration, it was decided that electronic effects should be investigated. A series of para substituted phenoxy derivatives of LiAlH_4 was examined with ketones I

and III. When the substituents were tert-butyl, hydrogen, and chlorine the results obtained with I and III showed no change of selectivity with substituent (Table 8). Electronic effects, within the series of similar hydrides, seem to be of little importance. Surprisingly the lithium triphenoxy aluminum hydrides are less selective towards III than LiAlH_4 .

Solvation Effects

It has been shown³⁰ that in THF, LiAlH_4 is primarily a solvent separated ion pair at 0.1 M while it is a contact ion pair in diethyl ether at the same concentration. It was shown³⁰ that four THF molecules will specifically solvate the lithium cation in diethyl ether solution. It was further suggested³⁰ that the difference in selectivity of LiAlH_4 in diethyl ether and THF may be attributed to the nature of the ion pair present in solution.

Table 9 gives the results of reductions of III with LiAlH_4 and NaAlH_4 0.1 M in diethyl ether, THF, and DME. Results in THF and DME are similar for LiAlH_4 and NaAlH_4 . In diethyl ether, LiAlH_4 gives 14% less equatorial attack than in THF. The observed 68% equatorial attack in diethyl ether does not agree well with the reported⁵ value of 55%. However, reduction at 0.5 M gives 55%. Sodium aluminum hydride is insoluble in diethyl ether and gives only trace amounts of reaction. If solvation is important it was initially thought that NaAlH_4 in DME, a bidentate ligand, may differ from NaAlH_4 in THF as LiAlH_4 differs in THF and diethyl ether; however,

this is not the case. NaAlH_4 in THF and DME gives the same results.

Reduction of III by LiAlH_4 in the mixed solvent THF-diethyl ether was carried out as the ratio of THF to LiAlH_4 varied from 1 to 6:1. If the difference between LiAlH_4 in diethyl ether and THF is that one is a contact ion pair and the other is solvent separated the selectivity of LiAlH_4 should change sharply at $\text{THF/Li} = 4$. The first four moles of THF added to the diethyl ether solution of LiAlH_4 are reported³⁰ to specifically solvate the lithium cation. The selectivity does not break at any THF/Li ratio. Only a gradual change is observed (Table 10). This suggests that the increase in selectivity of LiAlH_4 in going from diethyl ether to THF as solvent is a medium effect rather than any specific solvation by THF.

Similar experiments were carried out by adding tetramethylethylenediamine (TMED) to LiAlH_4 in diethyl ether and diethyl ether-benzene mixtures. No change in selectivity with TMED/Li ratio (Table 11) was observed.

Table 12 summarizes the results of reducing III with LiAlH_4 , NaAlH_4 , and KAlH_4 in the presence of crown ethers. Dicyclohexyl-18-crown-6 and dibenzo-18-crown-6 strongly complex potassium and sodium ions. Initially the use of crown ethers was to check the theory that the selectivity of MAlH_4 depend on the solvation of the cation, that is, whether MAlH_4 is a contact or solvent separated ion pair. It was believed that

the crown ethers with NaAlH_4 and KAlH_4 should give solvent separated ion pairs and a selectivity similar to LiAlH_4 in THF. However, this was not observed. Instead the crown ethers lower the selectivities of NaAlH_4 and KAlH_4 towards III. The cation when complexed by a crown ether probably resembles the tetraalkylammonium ion, a large ion with the charge buried at the center. Thus, the selectivity follows the pattern the larger the cation the less selective:
 $\text{LiAlH}_4 > \text{NaAlH}_4 > \text{KAlH}_4 > \text{NR}_4\text{AlH}_4 \sim \text{NaAlH}_4$ or KAlH_4 with crown ether. A reaction was run with LiAlH_4 and dicyclohexyl-18-crown-6 even though this crown ether is not very specific for lithium ion. On mixing a white precipitate immediately form. No significant change in stereochemistry was observed.

Complexation of the cation of MAlH_4 by a crown ether probably removes it from any direct participation in the reaction, such as complexing the carbonyl oxygen. In diethyl ether or THF the cation may complex the ketone while associating with several solvent molecules. The degree and number of solvent molecules associated with M^+ could effect the stereochemistry. The experiment above where III was reduced in diethyl ether at varying THF:Li ratio was interpreted to show a medium effect rather than any specific solvation by THF. However, a true medium effect might be expected to give results about midway between pure diethyl ether and pure THF as solvents when the ratio of diethyl ether:THF is 1:1. Even at

36% THF in the solvent mixture the results (81% equatorial attack) was essentially the same as pure THF (82%). This can be explained by competitive solvation between THF and diethyl ether where THF, the stronger solvating agent, accounts for most of the solvation of LiAlH_4 in a solvent mixture 36-50% THF.

The Evaluation of Other Hydrides for Stereoselectivity.

The data concerning the stereochemistry of reduction of a series of ketones with HBeCl and AlH_3 in diethyl ether and LiAlH_4 , LiAlD_4 , and $\text{LiZnMe}_2\text{H}\cdot\text{AlH}_3$ in THF are tabulated in Table 13. The reactions were run at 0° at a concentration of 0.10 M.

The AlH_3 used in these studies is very unusual in that it is soluble in diethyl ether.³⁷ Results are similar to LiAlH_4 and AlH_3 in THF. Although it gives almost twice the amount of equatorial attack of 4-tert-butylcyclohexanone as LiAlH_4 , it is less selective toward camphor.

The $\text{LiZnMe}_2\text{H}\cdot\text{AlH}_3$ gave more equatorial attack on I and III than LiAlH_4 . There is no methylation product according to gas chromatographic analysis.

The results of LiAlH_4 and LiAlD_4 are the same. Therefore, there is no significant primary isotope effect affecting the stereoselectivity of LiAlH_4 reductions of ketones.

The new hydride HBeCl is quite similar to LiAlH_4 except for the reduction of 4-tert-butylcyclohexanone. It gives 46% equatorial attack which is comparable to $\text{LiAl}(\text{OCH}_3)_3\text{H}$,

44%. What causes HBeCl to have a larger steric requirement is not readily apparent. HBeCl in diethyl ether is a dimer associated via hydrogen bridge³⁷ bonds. The increased steric strain may then be attributed to HBeCl being a dimer, however, if this is the case the HBeCl should be more selective than LiAlH₄ towards V, but it is not. More detailed mechanistic information is necessary to convincingly explain these results.

Product Development Control and Recent Theories
of Stereochemical Control

The most prominent theories of stereochemical control for reduction of ketones by metal hydrides are product development control, steric approach control, and torsional strain. A strong case against product development control as a factor in stereochemical control for the reduction of cyclohexanones has been presented by Eliel¹⁵ and Klein.¹⁴ They showed that LiAl(OBu^t)₃H (absolute rates), and LiAlH₄ and NaBH₄ (relative rates) exhibit about equal rates of equatorial attack on a series of cyclohexanones with varying degrees of steric hindrance to axial attack.

The relative rate constants in Table 14 were taken from absolute rate data^{20,49} involving the reaction of NaBH₄ with cyclic and bicyclic ketones in isopropyl alcohol. The results show that the rates of equatorial attack on cyclohexanones and endo attack on 2-keto-bicyclo(2.2.1)heptanes are

retarded when the C-3 axial substituent of cyclohexanones and the syn C-7 substituent of the 2-keto-bicyclo(1.2.2)-heptanes are changed from hydrogens to methyl groups. Although possibly other reasons can be given, one obvious explanation which is consistent with the results is that the developing negative charge on oxygen (O^-) is more hindered by the methyl group than the hydrogen. The results may lend some validity to a late transition state or product development control but it does not prove that product development control governs the reduction of 4-tert-butylcyclohexanone by metal hydrides.

The results reported in Table 1 show that $LiAlH_4$ gives more axial attack on 4-tert-butylcyclohexanone (I) and more equatorial attack on 3,3,5-trimethylcyclohexanone (III) than $NaAlH_4$. If these results are explained in terms of product development control and steric approach control then $NaAlH_4$ in the case of I has an earlier transition state and in the case of III has a later transition state than $LiAlH_4$. However, it seems reasonable that $NaAlH_4$ would have a transition state which is consistently earlier or later than that of $LiAlH_4$ with all the ketones. If torsional strain and steric approach control are used to explain the results of $NaAlH_4$ and $LiAlH_4$ with I and III there is no necessity to invoke $NaAlH_4$ having an earlier or later transition state $LiAlH_4$. For this reason and the work by Eliel¹⁵ and Klein,¹⁴ product development control was not discussed as a factor of stereo-

chemical control in the above discussions of results reported here.

Klein¹⁶ has recently suggested that hyperconjugation of the β C-C bonds of 4-tert-butylcyclohexanone with the π bond of the carbonyl group may cause the two faces of the carbonyl group to be non-equivalent, and would influence the stereochemistry of nucleophilic attack at the carbonyl group. Klein's scheme for orbital interactions is presented in Figure 1. He explained that the increased size of the lowest unoccupied molecular orbital (LUMO) on the axial side would allow for easier attack by a nucleophile such as a hydride in the absence of steric effects. However, it is not clear why the LUMO should be distorted towards the axial side. Klein gave the explanation that "interaction with the symmetrical C-C σ^* bond orbital makes the lobe of the orbital on the carbon of the carbonyl of the highest unoccupied molecular orbital smaller on the face containing the C-C bonds, thus avoiding electron repulsions, and therefore the orbitals of the LUMO are larger on the side of the β C-C bonds". It appears that the LUMO should be larger on the equatorial side, that is, in the direction of the larger back lobes of the C-C σ^* bonds, thus allowing the π^* bond and σ^* bond back lobes more overlap.

Klein's scheme in Figure 1 does predict equatorial attack on exocyclic double bonds by electrophiles which would attack the highest occupied molecular orbital (HOMO). This

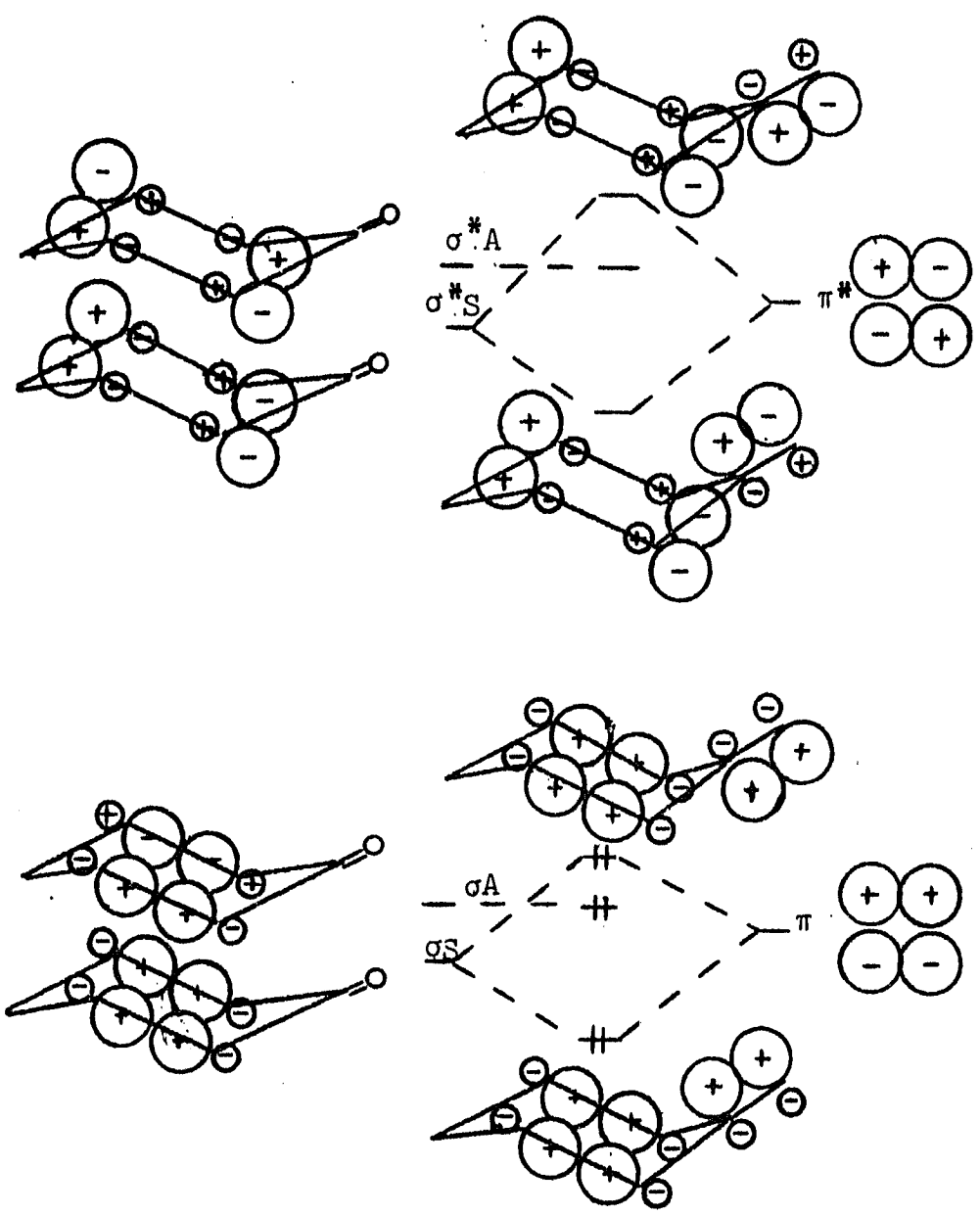


Figure 1. Hyperconjugation of the π Bond with the β C-C Bonds in Cyclohexanone (Reference 16).

is consistent with hydroboration of methylenecyclohexanes¹² where electrophilic attack by BH_3 is predominantly equatorial.

Hyperconjugation of β hydrogens is known to be important in the reduction of 4-tert-butylcyclohexanone with NaBH_4 because an inverse isotope effect ($k_{\text{H}}/k_{\text{D}} = .88$) has been observed⁵⁰ when deuterium atoms are substituted for the β -hydrogen atoms. Figure 2 represents a scheme for hyperconjugative interactions of the carbonyl π bond with the C-2 and C-6 axial hydrogens of 4-tert-butylcyclohexanone. The LUMO as drawn would favor axial attack by a nucleophile. However, the scheme in Figure 2 predicts axial attack by electrophiles on the highest occupied molecular orbital (HOMO), which would be inconsistent with hydroboration of methylenecyclohexanes.¹² In Figure 2 if only the back lobes of the axial C-H bonds at C-2 and C-6 are considered to interact with the π bond the scheme would predict correctly the direction of attack for nucleophiles and electrophiles.

Figures 1 and 2 are only a qualitative view of hyperconjugation. As drawn, both Figures 1 and 2 would predict axial attack by nucleophiles, therefore they were drawn using different rationales. If they were drawn using the same rationale, the two hyperconjugative effects would oppose each other and favor opposite directions of attack by nucleophiles and electrophiles because the C-C and C-H bonds are on opposite sides of the plane of the carbonyl group. Both Figures 1 and 2 have problems associated with them and it is difficult

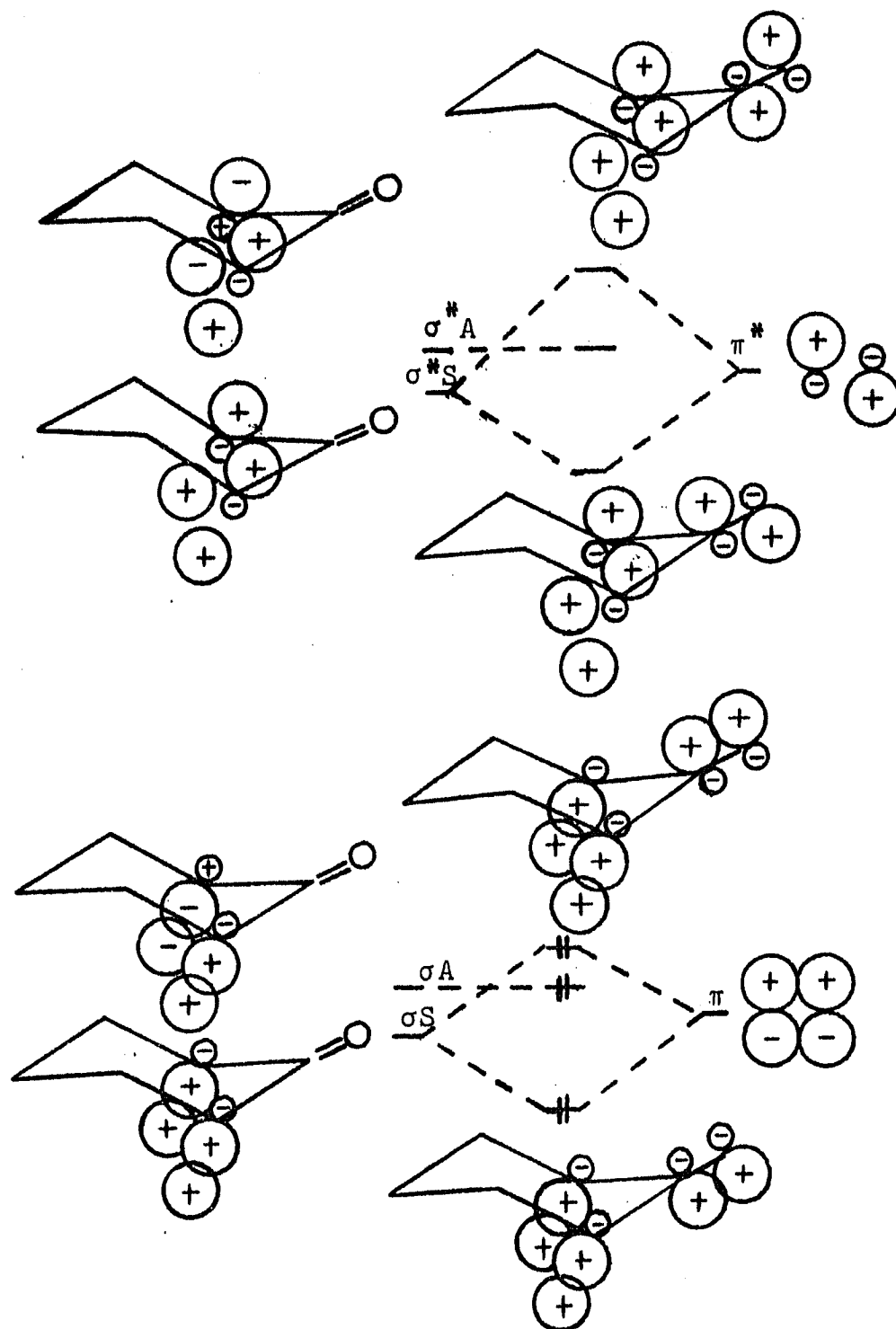
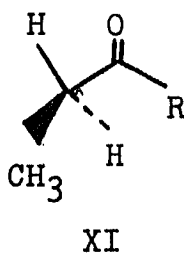
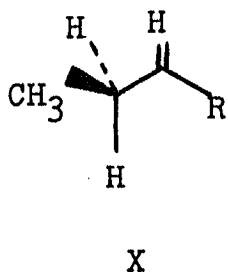


Figure 2. Hyperconjugation of the π Bond with the β C-H Bonds in Cyclohexanones.

to choose which more correctly demonstrates the importance of hyperconjugation. In Figure 1 the LUMO may be drawn incorrectly and the HOMO of Figure 2 predicts axial attack for electrophiles which is not observed for hydroboration of methylenecyclohexanes,¹² thus, a qualitative look at the molecular orbitals does not seem to resolve our understanding of stereochemical control of the reduction of cyclohexanones by metal hydrides. Maybe a quantitative evaluation would provide a clearer explanation of the importance of hyperconjugation in stereochemical control.

Ab initio (STO-3G) calculations have been performed¹⁷ on propanal and 2-butanone. Two fixed conformations X and XI were considered for each molecule. The π electron cloud



R = H, propanal

R = CH₃, 2-butanone

is distorted and the electron density is greater on one face than the other. If it is assumed that a nucleophile would preferentially attack the more positive side of the carbonyl group, the predicted side of attack on X and XI is the hydrogen side where the electron density is calculated to be the lowest. The predicted direction of attack is the same as steric approach control for each conformation. It was pointed

out that orbital factors may be more important at longer distances than steric factors. Calculations on 4-tert-butylcyclohexanone would need to show the π electron density greater on the equatorial (hydrogen) side in order to predict axial attack for metal hydrides. If conformation XI in which hydrogen eclipses the carbonyl group is allowed to roughly represent the cyclohexanone chair conformation the predicted direction of attack would appear to favor equatorial attack for metal hydride reduction which is not found experimentally.

Conclusion

The stereochemical evaluation of the MAlH_4 series as stereoselective reducing agents on selected model ketones show that results are dependent on M^+ . This suggests that the reducing agent is the ion pair M^+AlH_4^- and not just AlH_4^- . Comparison of LiAlH_4 to LiBH_4 showed LiBH_4 to be less selective towards III, IV, and V which may be explained on the basis that the BH_4^- ion is smaller than the AlH_4^- ion.

It was further demonstrated that the different conformations of a conformationally mobile ketone such as 2-methylcyclohexanone (II) are important in determining the stereochemical results. Because the degree to which different conformations of II participated in the reduction by MAlH_4 as M^+ varied from Li^+ to ClMg^+ to AlH_4Mg^+ , it was suggested that the cation may be complexing the carbonyl oxygen, interacting

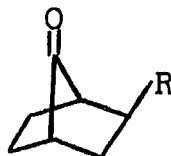
with the C-2 methyl group, and effecting a change in the conformation of the ketone during reduction.

The recently reported "compression effect" for controlling the stereochemistry of alkylation of cyclohexanones and cyclopentanones with excess $\text{Al}(\text{CH}_3)_3$ in benzene does not seem to be operative in the reduction of the ketones in this study with LiAlH_4 , ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$.

Contrary to previous reports, the selectivity of $\text{LiAl}(\text{OCH}_3)_3\text{H}$ is independent of concentration. Therefore, its greater selectivity over $\text{LiAl}(\text{OBu}^t)_3\text{H}$ does not depend on its greater degree of association at higher concentrations compared to $\text{Li}(\text{OBu}^t)_3\text{H}$ which is monomeric at all concentrations. No satisfactory explanation for the greater degree of selectivity of $\text{LiAl}(\text{OCH}_3)_3\text{H}$ compared to $\text{LiAl}(\text{OBu}^t)_3\text{H}$ could be found. Solvation and concentration studies conducted by reduction of 3,3,5-trimethylcyclohexanone (III) with LiAlH_4 , showed LiAlH_4 to be more selective at lower concentrations in THF, and more selective in THF than diethyl ether. However, the greater selectivity of LiAlH_4 in THF could not be attributed to any specific solvation of the lithium ion such as LiAlH_4 being a solvent separated ion pair in THF while a contact ion pair in diethyl ether.

Currently the three major concepts considered in stereochemical control of reduction of ketones by metal hydrides are steric approach control, product development control, and torsional strain. It would be of value to develop model sys-

tems where at least one of these concepts could be eliminated with certainty as a factor in the stereochemical control of the reduction. One such model system would be the exo-2-alkyl-7-norbornanone system.⁵¹ Torsional strain should be the



same for anti or syn attack by hydrides. The rates of anti attack could be measured as R is varied from hydrogen to methyl, etc. If equal rates of anti attack are observed, it would indicate an early transition state and the unimportance of product development control.

Table 1. Reductions of Some Representative Ketones
with a Series of Complex Aluminohydrides
(MAlH_4) in THF.

Ketone ^a	Hydride ^a	$\text{H}^-/\text{Ketone} = 6$		$\text{H}^-/\text{Ketone} = 1$	
		% Equatorial or Exo Attack	Yield ^b	% Equatorial or Exo Attack	Yield ^b
4-tert-butylcyclo- hexanone (I)	LiAlH_4	10	103	8	94 (2)
	NaAlH_4	13	104	12	98
	NR_4AlH_4	15	99	14	80 (12)
	$\text{Mg}(\text{AlH}_4)_2^c$	13	99 (2)	14	75 (14)
	ClMgAlH_4^d	10	86 (2)	10	85 (18)
2-methylcyclo- hexanone (II)	LiAlH_4	24	96	25	96
	NaAlH_4	29	91	28	96
	NR_4AlH_4	26	84	27	77 (11)
	$\text{Mg}(\text{AlH}_4)_2^c$	48	90	49	81 (10)
	$\text{Mg}(\text{AlH}_4)_2^e$	48	96	-	-
	ClMgAlH_4^d	36	94	43	83 (14)
3,3,5-trimethyl- cyclohexanone (III)	LiAlH_4	80	108	75	96 (6)

Table 1. Reductions of Some Representative Ketones with a Series of Complex Aluminohydrides (MAlH_4) in THF. (Continued)

Ketone ^a	Hydride ^a	$\text{H}^-/\text{Ketone} = 6$		$\text{H}^-/\text{Ketone} = 1$	
		% Equatorial or Exo Attack	Yield ^b	% Equatorial or Exo Attack	Yield ^b
3,3,5-trimethyl-cyclohexanone (III)	NaAlH_4	59	100	65	102 (2)
	NR_4AlH_4	55	106 (2)	55	80 (25)
	$\text{Mg}(\text{AlH}_4)_2^c$	61	102	56	86 (9)
	ClMgAlH_4^d	71	100	61	81 (18)
	LiAlH_4	91	98	90	97 (6)
Norcamphor (IV)	NaAlH_4	83	100	82	89 (11)
	NR_4AlH_4	74	106 (2)	76	73 (20)
	$\text{Mg}(\text{AlH}_4)_2^c$	87	102	86	94 (9)
Camphor (V)	ClMgAlH_4^d	92	98	88	83 (16)
	LiAlH_4	9	99	10	68 (26)
	NaAlH_4	12	98	12	79 (25)
	NR_4AlH_4	12	82 (26)	13	46 (57)
	$\text{Mg}(\text{AlH}_4)_2^c$	26	101	25	84 (16)

Table 1. Reductions of Some Representative Ketones with a Series of Complex Aluminohydrides ($MgAlH_4$) in THF. (Concluded)

Ketone ^a	Hydride ^a	$H^-/Ketone = 6$		$H^-/Ketone = 1$	
		% Equatorial or Exo Attack	Yield ^b	% Equatorial or Exo Attack	Yield ^b
Camphor (V)	$Mg(AlH_4)_2$ ^e	25	100	-	-
	$ClMgAlH_4$ ^d	19	96	22	69 (39)

^aThe initial concentration of hydride and ketone was 0.50 M. Ketone was added to hydride when $H^-/K = 6$. Hydride was added to ketone when $H^-/K = 1$. The reaction was carried out at 0°C and quenched after 2 hours.

^bAbsolute yield measured with an internal standard. The percent of recovered ketone is given in parentheses.

^c0.25 M ketone was added directly to the solid $Mg(AlH_4)_2$ in the ratios $H^-/ketone = 8$ and 1. The $Mg(AlH_4)_2$ contained NaCl. $Mg(AlH_4)_2$ has a small solubility in THF since it can be extracted from NaCl with THF.

^dThe initial concentrations of $ClMgAlH_4$ and ketone were 0.19 M and 0.25 M, respectively.

^eSame as (c) except $Mg(AlH_4)_2$ with no NaCl present.

Table 2. Percent Cis Alcohol from the Reaction of Complex Metal Hydrides with Cyclohexanones in THF.

Hydride ^a	I 4- <u>tert</u> -Butyl- cyclohexanone	II 2-Methyl cyclohexanone	VI cis-2-Methyl 4- <u>tert</u> -butyl- cyclohexanone
LiAlH ₄ ^b	10	24	19 ^c
LiAlH ₄	8	25	-
ClMgAlH ₄ ^b	10	36	21 ^c
ClMgAlH ₄	10	43	21 ^c
Mg(AlH ₄) ₂ ^b	13	48	27, ^c 26 ^d
Mg(AlH ₄) ₂	14	49	-

^aSee footnotes a, c, and d of Table 1.

^bExcess Hydride.

^cRatio measured by glc analysis.

^dRatio measured by nmr analysis.

Table 3. Reductions of Some Representative Ketones with LiBH_4 in THF.

Ketone ^a	H ⁻ /Ketone = 6 % Equatorial or <u>Exo</u> Attack	% Yield ^b	H ⁻ /Ketone = 1 % Equatorial or <u>Exo</u> Attack	% Yield ^b
I	7	97	8	92
II	29	92	36	95 (2)
III	53	95	60	96
IV	82	103	90	88
V	31	100 ^{c,d}	26	94 (6) ^{c,e}

^aSee footnote a of Table 1. I = 4-tert-butylcyclohexanone, II = 2-methylcyclohexanone, III = 3,3,5-trimethylcyclohexanone, IV = norcamphor, and V = camphor.

^bAbsolute yield measured with an internal standard. The percent of recovered ketone is given in parentheses.

^cRelative yield.

^d98% reaction by uv spectrophotometry in 9 days. Reaction was quenched after 10 days.

^e91% reaction by uv spectrophotometry in 31 days. Reaction was quenched after 31 days.

Table 4. Reduction of Cyclopentanones with LiAlH_4 , $\text{Mg}(\text{AlH}_4)_2$, and ClMgAlH_4 in THF.

Ketone ^a	Hydride ^a	$\text{H}^-/\text{Ketone} = 6$		$\text{H}^-/\text{Ketone} = 1$	
		% Cis Attack	Yield ^b	% Cis Attack	Yield ^b
2-methylcyclopentanone (VII)	LiAlH_4	84 ^{c,d}	100	84 ^{c,d}	100
	ClMgAlH_4	65 ^c	100	58 ^c	91
	$\text{Mg}(\text{AlH}_4)_2$	45 ^c	99	-	-
3-methylcyclopentanone (VIII)	LiAlH_4	27 ^d	100	29 ^d	92
	ClMgAlH_4	25 ^d	-	-	-
	$\text{Mg}(\text{AlH}_4)_2$	20 ^d	-	-	-
cis-3,4-dimethylcyclopentanone (IX)	LiAlH_4	10 ^d	100	10 ^d	90
	ClMgAlH_4	10 ^d	-	-	-
	$\text{Mg}(\text{AlH}_4)_2$	10 ^d	-	-	-

^aSee footnotes a, c, and d of Table 1.

^bRelative yields based on glc analysis.

^cRatio of products measured by glc analysis.

^dRatio of products measured by nmr in DMSO-d_6 .

Table 5. Reduction of 4-*tert*-Butylcyclohexanone, 3,3,5-Trimethylcyclohexanone and Camphor with Some Insoluble Complex Metal Hydrides.

Hydride ^a	Solvent	H ⁻ /Ketone	Conc. Ketone	% Equatorial or <u>Endo</u> Attack	% Yield ^b	Time (Hours)
4- <i>tert</i> -Butylcyclohexanone (I)						
MgH ₂	THF	2.0	0.077M	64	14 (76)	24
MgH ₂	THF	0.91	.13	65	6 (78)	24
NaZnH ₃	THF	2.7	.13	28	13 (50)	87
Li ₂ ZnH ₄	THF	4.1	.13	36	97 (trace)	87
NaMgH ₃	THF	4.0	.13	10	36 (39)	87
NR ₄ MgH ₃	THF	1.4	.13	trace	4 (72)	87
Na ₃ AlH ₆	Benzene	10.7	.13	30	28 (58)	87
Na ₃ AlH ₆	THF	11.0	.13	24	49 (42)	87
Na ₃ AlH ₆	THF	12.3	.13	15	25 ^c	3
Na ₃ AlH ₆	THF	12.3	.13	16	28 ^c	15
Na ₃ AlH ₆	THF	12.3	.13	22	39 ^c	43
Na ₃ AlH ₆	THF	12.3	.13	25	55 ^c	87

Table 5. Reduction of 4-tert-Butylcyclohexanone, 3,3,5-Trimethylcyclohexanone and Camphor with Some Insoluble Complex Metal Hydrides. (Continued)

Hydride ^a	Solvent	H ⁻ /Ketone	Conc. Ketone	% Equatorial or Endo Attack	% Yield ^b	Time (Hours)
3,3,5-Trimethylcyclohexanone (III)						
MgH ₂	THF	2.0	.046	45	23 (79)	24
MgH ₂	THF	1.5 ^d	.062	20	12 (94)	24
Na ₃ AlH ₆	THF	6.2	.13	75	82 (17)	85
Na ₃ AlH ₆	Benzene	6.3	.19	65	68 (5)	85
Na ₃ AlH ₆	THF	5.0 ^e	.42	68	25 (61)	85
Na ₃ AlH ₆	Benzene	4.8 ^f	.33	61	37 (45)	85
Camphor (V)						
MgH ₂	THF	2.0	.046	79	24 (74)	28
Na ₃ AlH ₆	THF	6.7	.13	90	64 (46)	85
Na ₄ AlH ₆	Benzene	6.1	.13	75	19 (85)	85

Table 5. Reduction of 4-tert-Butylcyclohexanone, 3,3,5-Trimethylcyclohexanone and Camphor with Some Insoluble Complex Metal Hydrides. (Concluded)

-
- ^a Reaction mixture stirred continuously at room temperature.
- ^b Absolute yield measured with an internal standard. The percent of recovered ketone is given in parentheses.
- ^c Relative yields.
- ^d 1.28 mmoles of ketone and 1.76 mmoles of alcohol (75% axial) was added to 2.28 mmoles of MgH_2 .
- ^e 3.90 mmoles of ketone and 5.38 mmoles of alcohol (70% axial) was added to 7.70 mmoles of Na_3AlH_6 .
- ^f 3.90 mmoles of ketone and 3.16 mmoles of alcohol (70% axial) was added to 5.64 mmoles of Na_3AlH_6 .

Table 6. Reduction of 4-tert-Butylcyclohexanone and 2-Methylcyclohexane with $\text{LiAl(OBu}^t)_3\text{H}$, $\text{LiAl(OCH}_2)_3\text{H}$ and LiAlH_4 at Varying Concentrations in THF.

Ketone ^a	Hydride ^a	Initial Conc. Hydride	% Equatorial Attack	Yield
4-tert-butylcyclohexanone (I)	$\text{LiAl(OBu}^t)_3\text{H}$.0051 M	10	112
		.055	10	114 (1)
		.51	11	113
	$\text{LiAl(OCH}_2)_3\text{H}$.0051	41	85 (14)
		.055	41	119
		.58	44	97
	LiAlH_4	.0049	8	105 (1)
		.056	9	103
		.62	10	112

Table 6. Reduction of 4-tert-Butylcyclohexanone and 2-Methylcyclohexane with $\text{LiAl}(\text{O}i\text{Bu})_3\text{H}$, $\text{LiAl}(\text{OCH}_3)_3\text{H}$ and LiAlH_4 at Varying Concentrations in THF. (Continued)

Ketone ^a	Hydride ^a	Initial Conc. Hydride	% Equatorial Attack	Yield
2-methylcyclohexanone (II)	$\text{LiAl}(\text{O}i\text{Bu})_3\text{H}$.0051 M	35	66 ^b
		.055	34	103
		.51	36	99
	$\text{LiAl}(\text{OCH}_3)_3\text{H}$.0032	65 (63) ^c	40 ^b
		.0051	63 ^d	76 ^b
		.0053	68 (68) ^c	57 ^b
		.0080	66 (67) ^c	37 ^b
	LiAlH_4	.055	65 ^d	97
		.58	63 ^d	109
		.0049	19	65
		.056	21	100
		.62	24	109

Table 6. Reduction of 4-tert-Butylcyclohexanone and 2-Methylcyclohexane with $\text{LiAl(OBu}^t)_3\text{H}$, $\text{LiAl(OCH}_3)_3\text{H}$ and LiAlH_4 at Varying Concentrations in THF. (Concluded)

^a0.50 Ketone added to hydride at 0°C in THF. Ratio $\text{H}^-/\text{K} = 1.5$. The reaction was quenched after 2 hours.

^bReaction mixture was concentrated after quenching with an aspirator. Some of the product was probably lost under reduced pressure which accounts for the low yield.

^cThe value in parentheses was obtained with a flame ionization glc before the solution was concentrated.

^dSecond preparation of $\text{LiAl(OCH}_3)_3\text{H}$.

Table 7. Reaction of 3,3,5-Trimethylcyclohexanone with LiAlH_4 and NaAlH_4 at Various Concentrations in THF.

Hydride ^a	Initial Conc. Hydride ^a	Ratio H^-/Ketone	% Equatorial Attack	Yield ^b
LiAlH_4^c	.0020 <u>M</u>	8.0	89.4	106 (3)
	.012	6.0	82.4	105 (2)
	.051	5.8	79.4	107
	.11	5.8	79.9	98
	.29	6.0	76.8	98
	.38	6.0	75.6	102
	.73	5.8	75.0	99
	1.0	5.8	74.6	98
NaAlH_4^c	.012	6.4	68.2	105 (2)
	.055	5.9	60.4	108
	.12	5.9	57.7	103
	.39	6.2	55.5	104
	1.0	6.7	51.3	100
LiAlH_4^d	.0097	1.0	76.4	80 (8)
	.048	1.0	75.7	96 (4)
	.048	1.0	76.5	92 (4)
	.12	1.0	73.6	95 (2)
	.20	1.0	71.9	97
	.20	1.0	70.7	99
	.20	1.0	71.0	98
	.50	1.0	65.5	95

Table 7. Reaction of 3,3,5-Trimethylcyclohexanone with LiAlH_4 and NaAlH_4 at Various Concentrations in THF. (Continued)

^aReaction at 0°C in THF for 2 hours.

^bAbsolute yield measured with an internal standard. The percent of recovered ketones is given in parentheses.

^c1.0 M ketone added to hydride.

^d1.0 M LiAlH_4 added to ketone. The concentration of LiAlH_4 reported is based on the resulting volume of reaction mixture.

Table 8. Reduction of 4-tert-Butylcyclohexanone and 3,3,5-Trimethylcyclohexanone with Lithium Triaryloxy Aluminohydrides in THF.

Aryloxy Group	% Equatorial Attack ^a	% Yield ^b
4- <u>tert</u> -Butylcyclohexanone		
4-chlorophenoxy ^c	8	101
phenoxy ^d	7	92
4- <u>tert</u> -butylphenoxy ^e	7	92
3,3,5-Trimethylcyclohexanone		
4-chlorophenoxy ^c	65	92
phenoxy ^d	63	92
4- <u>tert</u> -butylphenoxy ^e	61	94

^aThe ratio of H⁻/ketone in all cases was 1.5. 0.50 M ketone was added to the hydride at 0°C. The reaction was quenched after 2 hours. The phenol was extracted with NaOH before glc analysis was carried out.

^bAbsolute yield measured with an internal standard.

^c0.40 M initial concentration.

^d0.37 M initial concentration.

^e0.39 M initial concentration.

Table 9. Reduction of 3,3,5-Trimethylcyclohexanone by LiAlH_4 in Diethyl Ether, THF, DME and by NaAlH_4 in THF and DME.

Hydride ^a	Solvent	Conc.	% Equatorial Attack
LiAlH_4	Ether	0.1 <u>M</u>	68
LiAlH_4	Ether	0.5	55
LiAlH_4	THF	0.1	82
LiAlH_4	DME	0.1	78
NaAlH_4	THF	0.1	64
NaAlH_4	DME	0.1	63

^aThe ketone in the appropriate solvent was added to the hydride solution ($\text{H}^-/\text{ketone} = 6$). The reaction was quenched after 2 hours at 0° .

Table 10. Reduction of 3,3,5-Trimethylcyclohexanone in Diethyl Ether by LiAlH_4 at Varying THF:Li Ratios.

THF/Li ^a	% THF v/v	% Equatorial Attack
0	0	68
1	0.82	68
2	1.6	69
3	2.5	69
4	3.3	70
5	4.1	69
6	4.9	69
7	5.7	70
8	6.6	69
10	8.2	71
15	12	75
18	15	76
24	20	76
30	25	79
36	30	79
43	35	81
61	50	81
THF	100	82

^aThe ketone in diethyl ether solvent was added to the hydride in diethyl ether-THF mixed solvent ($\text{H}^-/\text{ketone} = 6$). The initial concentration of the ketone and hydride was 0.10 M. Temperature 0°. Reaction time was 2 hours.

Table 11. Reduction of 3,3,5-Trimethylcyclohexanone by LiAlH_4 in Diethyl Ether and Diethyl Ether-Benzene Mixtures at Varying TMED:Li Ratios.

Solvent	TMED/Li	Solubility of Complex	% Equatorial Attack
ether	0.5	sol	68
ether	1.0	sol	69
ether	2.0	insol	71
ether	4.0	insol	72
ether/benzene 93%	0.5	insol	64
ether/benzene 85%	1.0	sol	68
ether/benzene 94%	2.0	sol	70
ether/benzene 94%	4.0	sol	71

^aKetone in diethyl ether added to LiAlH_4 in diethyl ether or ketone in benzene added to LiAlH_4 in mixed solvent ($\text{H}^-/\text{ketone} = 6$). The initial concentration of the ketone and hydride was 0.10 M. Temperature 0°. Reaction time was 2 hours.

Table 12. The Reduction of 3,3,5-Trimethylcyclohexanone by LiAlH_4 , NaAlH_4 , and KAlH_4 in the Presence of Crown Ethers.

Hydride ^a	Conc.	Crown ^b Ether	Solvent	Crown Ether M ⁺	% Equatorial Attack
LiAlH_4	.1M	-	ether	-	68
"	.1	A ^c	ether	1.0	78
"	.1	A ^d	ether	1.0	72
NaAlH_4	.1	-	THF	-	68
"	.1	A ^c	THF	1.1	61
"	.1	A ^c	THF	1.1	64
"	.1	A ^d	THF	1.2	69
"	.1	B ^d	THF	1.1	51
"	.1	B ^d	THF	1.4	44
LiAlH_4	.01	-	THF	-	82
NaAlH_4	.01	-	THF	-	68
KAlH_4	.007	-	THF	-	60
KAlH_4	.007	A ^c	THF	1.1	59
"	.1 ^e	A ^c	THF	1.8	51
"	.007	A ^c	THF	2.2	50
"	.007	B ^d	THF	1.1	57
"	.007	B ^d	THF	2.4	44

^aKetone was added to hydride ($\text{H}^-/\text{ketone} = 6$). Temperature 0° . Reaction time was 2 hours.

^bA = dicyclohexyl-18-crown-6; B = dibenzo-18-crown-6.

^cFrom H. O. House. ^dFrom J. D. Cram

^e KAlH_4 weighed out as solid to give .1 M solution but solubility is .007 M.

Table 13. Reduction of Some Representative Ketones with Some Soluble Metal Hydrides.

Ketone ^{a,b,c}	Hydride ^c	H ⁻ / Ketone	Solvent	% Equatorial or <u>Exo</u> Attack
I	HBeCl	2	ether	46
I	HBeCl	1	ether	43
III	HBeCl	2	ether	83
III	HBeCl	1	ether	85
IV	HBeCl	2	ether	92
V	HBeCl	2	ether	14
I	LiAlH ₄	6	THF	10
I	LiAlD ₄	6	THF	9
III	LiAlH ₄	6	THF	82
III	LiAlD ₄	6	THF	85
IV	LiAlH ₄	6	THF	93
IV	LiAlD ₄	6	THF	92
V	LiAlH ₄	6	THF	8
V	LiAlD ₄	6	THF	8
I	AlH ₃	4.5	ether	19
I	AlH ₃	1	ether	18
III	AlH ₃	4.5	ether	77
III	AlH ₃	1	ether	66
IV	AlH ₃	4.5	ether	96
V	AlH ₃	4.5	ether	18
I	LiZn(CH ₃) ₂ H·AlH ₃	6	THF	17

Table 13. Reduction of Some Representative Ketones
with Some Soluble Metal Hydrides.
(Continued)

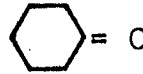
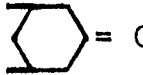
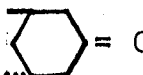
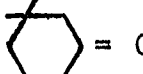
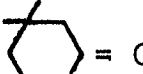


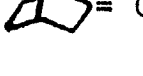

Ketone ^{a,b,c}	Hydride ^c	H ⁻ / Ketone	Solvent	% Equatorial or <u>Exo</u> Attack
III	LiZn(CH ₃) ₂ H·AlH ₃	6	THF	93

^aKetone in the appropriate solvent was added to the hydride. Temperature 0°. Reaction time was 2 hours.

^bI = 4-tert-butylcyclohexanone, III = 3,3,5-trimethylcyclohexanone, IV = norcamphor, V = camphor.

^cAll hydrides and ketones were initially 0.10 M.

Table 14. Relative Rate Constants for the Reaction of Selected Ketones with NaBH_4 in Isopropyl Alcohol.

Ketone ^a	k_{Total}	k^b Axial or Endo	k^b Equatorial or Exo
1.  = 0	100	(86) ^c	(14) ^c
2.  = 0	64	55	9.0
3.  = 0	2.5	(1.0) ^d	(1.5) ^d
4.  = 0	2.0	0.8	1.2
5.  = 0	0.14	-	(0.14)
6.  = 0	100	14	86
7.  = 0	0.48	0.38	0.10
8.  = 0	11	1.7	9.3
9.  = 0	0.050	0.043	0.007

^aEntries 1-5 from reference²⁰; Entries 6-9 from reference⁴⁹; Entries 1-5 relative cyclohexanone = 100; Entries 6-9 relative norcamphor = 100.

^bDetermined from isomeric ratio of product.

^cAssumed same isomeric ratio of product as entry 2.

^dAssumed same isomeric ratio of product as entry 4.

LITERATURE CITED*

1. For recent review see H. O. House, "Modern Synthetic Organic Reactions," W. A. Benjamin, Inc., New York 1972, p. 45 ff.
2. J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1972, p. 116 ff.
3. E. L. Eliel and R. S. Ro, J. Amer. Chem. Soc., 79, 5992 (1957).
4. P. T. Lansbury and R. E. MacLeay, J. Org. Chem., 28, 1940 (1963).
5. H. Haubenstein and E. L. Eliel, J. Amer. Chem. Soc., 84, 2363 (1962).
6. W. G. Dauben, G. J. Fonken, and D. S. Noyce, J. Amer. Chem. Soc., 78, 2579 (1956).
7. H. C. Brown and H. R. Deck, J. Amer. Chem. Soc., 87, 5620 (1965).
8. M. Cherest, H. Felkin, and N. Prudent, Tetrahedron Lett., 2199 (1968).
9. M. Cherest and H. Felkin, Tetrahedron Lett., 2205 (1968).
10. M. Cherest, H. Felkin, and C. Frajerman, Tetrahedron Lett., 379 (1971).
11. M. Cherest and H. Felkin, Tetrahedron Lett., 383 (1971).
12. J. Klein and D. Lichtenburg, J. Org. Chem., 35, 2654 (1970).
13. J-C Richer, J. Org. Chem., 30, 324 (1964).
14. J. Klein, E. Dunkelblum, E. L. Eliel, and Y. Senda, Tetrahedron Lett., 6127 (1968).

* For the complete titles of all journals referred to, see Access, 1969.

15. E. L. Eliel and Y. Senda, Tetrahedron, 26, 2411 (1970).
16. J. Klein, Tetrahedron Lett., 4307 (1973).
17. N. T. Anh, O. Eisenstein, J-M Lefour and M-E Tran Huu Dau, J. Amer. Chem. Soc., 95, 6146 (1973).
18. E. R. Garrett and D. A. Lyttle, J. Amer. Chem. Soc., 75, 6051 (1953).
19. H. C. Brown, O. H. Wheeler, and K. Ichikawa, Tetrahedron, 1, (1957).
20. B. Rickborn and M. T. Wuesthoff, J. Amer. Chem. Soc., 92, 6894 (1970).
21. J. Klein and E. Dunkelblum, Tetrahedron, 23, 205 (1967).
22. J. Klein and E. Dunkelblum, Israel J. Chem., 5, 181 (1967).
23. D. C. Ayres, D. N. Kirk, and R. Sawdaye, J. Chem. Soc., (B), 1133 (1970).
24. H. C. Brown, E. J. Mead, and B. C. S. Rao, J. Amer. Chem. Soc., 77, 6209 (1955).
25. H. C. Brown and K. Ichikawa, J. Amer. Chem. Soc., 83, 4372 (1961).
26. A. E. Finholt, E. C. Jacobson, A. E. Ogard, and P. Thompson, J. Amer. Chem. Soc., 77, 4163 (1955).
27. O. Strouf, Coll. Czech. Chem. Comm., 37, 2693 (1972), and references therein.
28. D. C. Ayres and W. Sawdaye, Chem. Commun., 527 (1966).
29. E. C. Ashby, J. P. Sevenair, and F. R. Dobbs, J. Org. Chem., 36, 197 (1971).
30. E. C. Ashby, F. R. Dobbs, and H. P. Hopkins, Jr., J. Amer. Chem. Soc., 95, 2823 (1973), and unpublished results.
31. R. Ehrlich, A. R. Young, II, and D. D. Perry, Inorg. Chem., 4, 758 (1965).
32. E. C. Ashby, R. D. Schwartz, and B. D. James, Inorg. Chem., 9, 325 (1970).

33. E. C. Ashby and R. D. Schwartz, Inorg. Chem., 10, 355 (1971).
34. E. C. Ashby and B. D. James, Inorg. Chem., 8, 2468 (1969).
35. E. C. Ashby and J. Watkins, unpublished results.
36. E. C. Ashby, S. Srivastava, and J. Watkins, unpublished results.
37. E. C. Ashby, J. R. Sanders, P. Claudy, and R. Schwartz, J. Amer. Chem. Soc., 95, 6485 (1973).
38. J-P. Battioni and W. Chodkiewiz, Bull. Soc. Chim. Fr., 1824 (1971).
39. G. Chauviere, Z. Welvart, D. Eugene, and J-C. Richer, Can. J. Chem., 47, 3285 (1969).
40. S. R. Landor and J. P. Regan, J. Chem. Soc., (C), 1159 (1967).
41. A. V. Kamernitzky and A. A. Akhrem, Tetrahedron, 18, 705 (1962).
42. E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publisher, New York, 1972, p. 113.
43. E. C. Ashby, J. R. Boone, and J. P. Oliver, J. Amer. Chem. Soc., 95, 5427 (1973).
44. "CRC Handbook of Chemistry and Physics," 47 ed., p. F-124 (1966).
45. D. M. S. Wheeler and J. W. Huffman, Experientia, 16, 516 (1960).
46. J. Laemmle, E. C. Ashby, and P. V. Roling, J. Org. Chem., 38, 2526 (1973).
47. N. L. Allinger, M. T. Tribble, and M. A. Miller, Tetrahedron, 28, 1173 (1972).
48. H. C. Brown and Nung Min Yoon, J. Amer. Chem. Soc., 88, 1464 (1966).
49. H. C. Brown and J. Muzzio, J. Amer. Chem. Soc., 88, 2811 (1966).

50. P. Geneste and G. Lamaty, Bull. Soc. Chim. Fr., 669 (1968).
51. E. C. Ashby and J. Laemmle, in press.

PART II

KINETICS OF METAL HYDRIDE REDUCTION OF KETONES

CHAPTER I

INTRODUCTION

Background

Many studies concerning stereoselective reduction of ketones by complex metal hydrides have been conducted over the past 30 years. There is still much discussion over those factors that control the stereochemistry of this reaction.¹⁻³

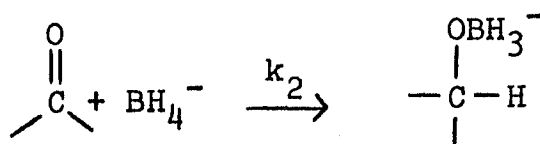
After studying the stereochemistry of metal hydride reduction of a number cyclic and bicyclic ketones under varying conditions of cation and anion size, concentration, stoichiometry, solvent and temperature,⁴ it is clear that more information is needed about the transition state of the reaction to explain the stereochemical results. Since the nature of the reagent and the mechanism of the reaction are both essential in establishing the nature of the transition state, it is clear that the composition of LiAlH_4 in ether solvents and the mechanism of LiAlH_4 reduction of a model ketone is a good starting point in an attempt to understand the stereochemistry of the reaction.

The composition of LiAlH_4 and other complex metal hydrides in ether solvents⁵ have recently been studied by conductance measurements of the type first reported by Hogen-

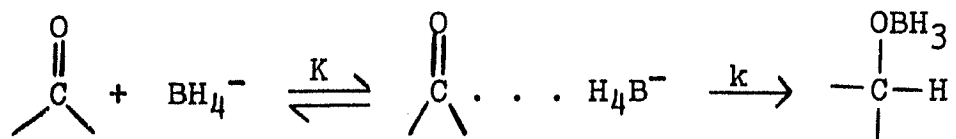
Esch and Smid.⁶ The results of the conductance studies of LiAlH_4 in THF indicate the presence of free ions and ion pairs (solvent separated) in dilute solution (10^{-2} - 10^{-6}M) and triple ions in more concentrated solution (10^{-1}M and greater).

Some mechanistic studies involving kinetics have been carried out on the reaction of complex metal hydrides with ketones.^{3,7-16} Most of these studies involve the reaction of NaBH_4 in isopropyl alcohol; however, some recent competitive rate kinetic studies have been conducted involving alumino hydrides.^{3,15,16}

Garrett and Lyttle¹⁴ in 1953 showed that reduction of ketones by NaBH_4 is a second order reaction; first order in each reactant. Brown and coworkers have verified these results.¹³ Brown and coworkers have also shown that the transfer of the first hydride from boron is the rate controlling step and transfer of the remaining three hydrides from the intermediate alkoxyborohydrides are faster steps.^{13,17} The suggestion was made that the kinetic results could be explained by direct reaction of borohydride ion and the ketone, or the results could be represented by the product of an

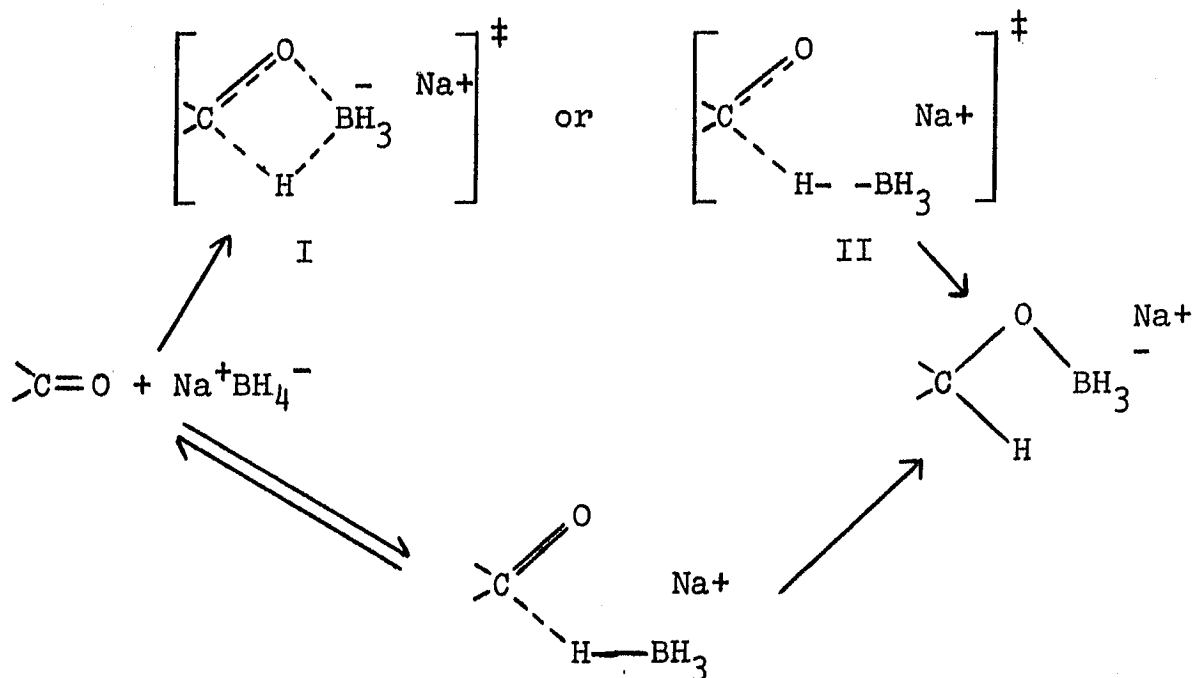


equilibrium constant for the association of borohydride ion and the ketone, and the rate constant for the subsequent transfer of a hydride ion to the carbonyl group ($k_2 = Kk$).



Several Hammett studies have been conducted on the reaction of NaBH_4 with substituted fluorenones^{10,11} and acetophenones.⁹ The large positive ρ values, + 2.65 and + 3.06, confirm the rate determining step as a nucleophilic attack of the borohydride ion on the carbonyl carbon atom resulting in a negatively charged transition state. Correlation of the rates of NaBH_4 reaction with several arylalkyl and alkyl methyl ketones with Taft's equation for systems involving dependence on both polar and steric effects, showed that steric effects appear to exhibit a dominant role in the reaction. Two pathways suggested for the reaction were direct reaction or formation of an initial complex followed by an internal hydride transfer.

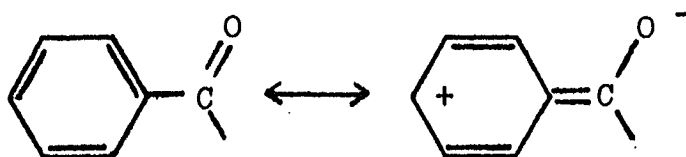
Geneste and Lamaty²⁰ supported transition state I because reduction of acetone by NaBH_4 and NaBD_4 gives an inverse isotope effect, $K_{\text{H}}/K_{\text{D}} = 0.7$. They viewed the reaction as an electrophilic attack on the B-H bond, thus a four center transition state such as I was suggested as most likely.



In 1955 Brown reported¹⁸ that lithium and magnesium salts catalyze the reduction of esters by NaBH_4 in isopropyl alcohol and diglyme, demonstrating that the reaction of the borohydride ion is not independent of the metal ion. In 1961 Brown¹⁹ reported no observable reduction of acetone by NaBH_4 in aprotic solvents such as acetonitrile, pyridine, dimethylformamide, and diglyme. He also reported that LiBH_4 reacts three times faster than NaBH_4 with acetone in isopropyl alcohol, but reacts at the same rate in water. This observation was interpreted to mean that, in water, borohydride ion is the reducing agent but in isopropyl alcohol the ion pair (M^+BH_4^-) is the reducing agent. Therefore in order for sodium borohydride to react with a carbonyl compound, it must be in the presence of an ionizing solvent such as water or an alco-

hol and in such a solvent the presence of the lithium ion will catalyze the reaction, presumably by forming LiBH_4 . Lithium borohydride will reduce ketones in THF as shown in the first part of this thesis or other aprotic solvents.^{21,22} The lithium ion may assist in the reaction by polarization of the carbonyl group or the borohydride ion as the hydride is transferred.¹⁹

Lansbury^{21,22} has reported that diaryl ketones are reduced faster than dialkyl ketones by LiBH_4 in pyridine, but that the reverse rate order is found when diglyme is the solvent. In both solvents diaryl ketones are reduced faster than dialkyl ketones by NaBH_4 . When alcohols are used as solvents, both LiBH_4 and NaBH_4 reduce dialkyl ketones faster than diaryl ketones. Thus, a greater reactivity is observed for the diaryl ketone when no electrophilic catalysis is available, that is when aprotic solvents (which cannot hydrogen bond to the carbonyl group) are used or when the lithium ion is effectively tied up by pyridine solvent. Under these conditions dipolar resonance contributions cannot be stabilized by coordination of the carbonyl oxygen with an electro-



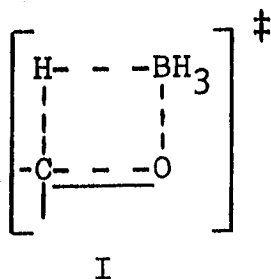
phile, thus the inductive electron withdrawing effect of the aryl groups are dominant and diaryl ketones are more reactive than dialkyl ketones. These results are in agreement with Brown's results where it was found that the lithium ion catalyzes the reduction of esters¹⁸ and ketones¹⁹ by NaBH_4 in isopropyl alcohol.

In summary then, reduction of ketones by metal borohydrides is first order in each reactant, involves a nucleophilic attack of the borohydride ion at the carbonyl carbon atom, and is dependent in some manner on the metal cation present, possibly by coordination of the carbonyl oxygen. However, it is still uncertain whether the carbonyl oxygen in the transition state is associated with the boron atom (four-centered transition state), with the metal cation (six-centered transition state), or neither, and where the transition state lies along the reaction coordinate. Recently several papers have addressed themselves to the latter point. The position of the transition state along the reaction coordinate is of significant importance in determining the stereochemical control of reduction reactions since a late transition state would support product development control and an early transition state would support torsional strain or other electronic effects.

Reasons for supporting or not supporting product development control (late transition state) in metal hydride reduction of ketones have been outlined and discussed.³ Reasons

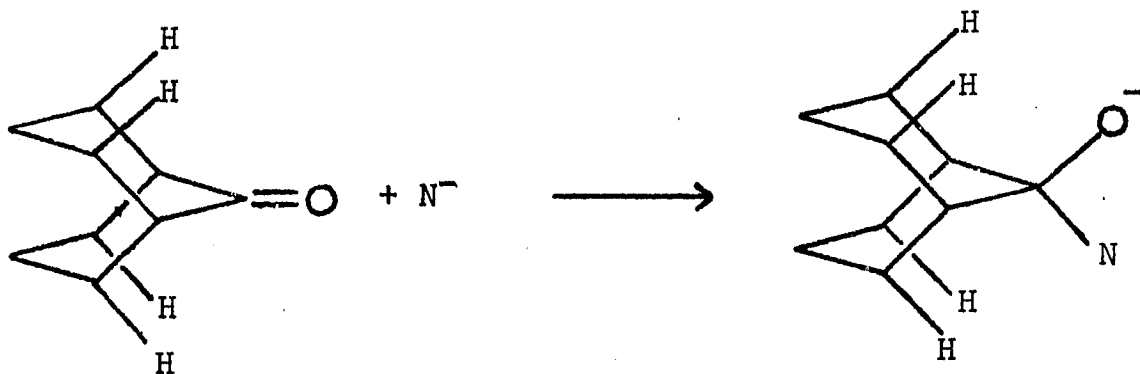
for not supporting are: (1) that the high exothermicity and low activation energy of the reaction suggest an early transition state according to the Hammond postulate; and (2) the equilibrium concentration of the aluminum alkoxide of 4-tert-butylcyclohexanol in THF is 82% trans which is less than the amount of trans product (89%) obtained on reduction of 4-tert-butylcyclohexanone by LiAlH_4 in THF. Supporting reasons were: (1) Cyclopentanone reacts slower than cyclohexanone with sodium borohydride, which when explained on the basis of I-strain, would require a substantially sp^3 hybridized carbonyl carbon atom in the transition state; (2) a large ρ value for reduction of substituted acetophenones and fluorenones would suggest a late transition state; and (3) an inverse isotope effect observed with NaBD_4 reduction of ketones has been interpreted to suggest a late transition state. However, concerning the latter point, the same result has also been interpreted supporting an early transition state.

The relative rate studies of Eliel³ showed nearly equal rates of attack on the equatorial side of a series of substituted cyclohexanones using several different hydrides including NaBH_4 and LiAlH_4 . This was interpreted to suggest that product development control in these reductions is of minor importance. In regard to the transition state (I) postulated by Geneste and Lamaty,²⁰ Eliel stated³ that it would explain the importance of I-strain observed in borohydride



reduction of cyclic ketones. Eliel further pointed out that such a transition does not necessarily require tetrahedral geometry despite a substantial degree of C-H bond formation and sp^3 hybridization of the carbon atom of the carbonyl group. It was concluded that reactant-like geometry of the transition state explains the absence of product development control which is what Eliel observed.

Geneste and Lamaty^{8,20} support a late transition state for borohydride reduction of ketones. They have supposedly presented data which "prove beyond any reasonable doubt that the transition state is product-like" for these reactions. Adamantanone presents two equal sides (which are like the axial side of 4-tert-butylcyclohexanone) for a nucleophile to



attack. If the transition state is product-like the carbonyl carbon atom will be sp^3 hybridized and both N and O^- will be in an axial position. If N is small as in borohydride reduction the only important interaction is 1,3 diaxial interaction of O^- with axial hydrogens. Thus, this late transition state would resemble equatorial attack on 4-tert-butylcyclohexanone. If this is true then the rate constant (k_α) of attack on adamantanone would equal twice the rate constant (k_e) of equatorial attack on 4-tert-butylcyclohexanone by borohydride. They observed $k_\alpha = 5.14$, $k_a = 8.55$ (axial attack on 4-tert-butylcyclohexanone), and $k_e = 2.15$ ($1 \text{ mole}^{-1} \text{ minute}^{-1}$). Therefore, $k_\alpha \approx 2k_e$ and thus the conclusion of a late transition state.

On the other hand, Wigfield and Phelps⁷ have offered an alternative explanation for the results of Geneste and Lamaty. They pointed out that attack on adamantanone is axial to one ring but equatorial to the other. Therefore attack on adamantanone is the same as attack on the least favored side of 4-tert-butylcyclohexanone and the prediction would be $k_\alpha = 2 k(\text{least favored})$. Thus, Geneste and Lamaty's results are not unambiguous proof of a late transition state in borohydride reduction of ketones.

Wigfield and Phelps^{7,25} conducted a deuterium kinetic isotope study for the reduction of a series of cyclohexanones with various degrees of steric hindrance using NaBH_4 and NaBD_4 . The ratios of k_H/k_D were small, inverse ($\sim .7$), and essential-

ly constant for all the cyclohexanones despite changes in the ratio of axial to equatorial attack. This suggested that the transition state has the same degree of bond making and bond breaking regardless of the direction of attack which would not be in accord with steric-approach-control-product-development-control theory for hindered and unhindered cyclohexanones. The results therefore support rationalizing product ratio in terms of steric hindrance and torsional strain, which are based on early transition states. The primary isotope effect being small and masked by secondary effects was pointed out to be consistent with an early transition state but not proof thereof.

No kinetic studies have been reported for reduction of a ketone by lithium aluminum hydride, although some work with lithium tri-tert-butoxyaluminumhydride $[\text{LiAl}(\text{OBu}^t)_3\text{H}]$ has been reported.^{15,16} The degree to which the mechanistic information known about borohydride reduction of ketones can be applied to the aluminumhydride reduction is not known. The second, third, and fourth stages of reduction with the aluminumhydride ion is reported^{26,27} to be slower than the first step while the opposite is known to be the case for borohydride reduction.^{13,17} It has been proposed²⁷ that reduction by the alkoxy aluminumhydride intermediates is minor because these compounds rapidly disproportionate to regenerate the aluminumhydride ion (AlH_4^-). On the other hand, it is known that many alkoxy-aluminumhydrides are stable to disproportionation.²⁸

Thus, for aluminohydride reduction, the AlH_4^- ion may or may not be the only major reducing species while for borohydride reduction the alkoxy intermediates are important reducing species. These mechanistic differences for the latter stages of reduction do not indicate anything about the differences or similarities of the mechanisms of the initial step, attack of ketone by M^+BH_4^- and M^+AlH_4^- .

Rates of reduction of a series of cyclohexanones using a large excess of $\text{LiAl}(\text{OBu}^t)_3\text{H}$ showed the reaction to be first order in ketone and first order in $\text{LiAl}(\text{OBu}^t)_3\text{H}$.¹⁶ The similarity in the rate of equatorial attack on the cyclohexanones was interpreted to rule out product development control as a factor in the stereochemical control of the reaction. The difference in the total rate of reduction of the cyclohexanones was later interpreted³ to show that complexing of the ketone by $\text{LiAl}(\text{OBu}^t)_3\text{H}$ is not rate determining since the rate of complexation of the cyclohexanones by $\text{LiAl}(\text{OBu}^t)_3\text{H}$ should be about the same. The manner of complexation was not specified. Competitive rate studies³ on a series of cyclohexanones by LiAlH_4 were also conducted. Possible conclusions have already been discussed above.

A series of substituted benzophenones,¹⁵ when reduced with $\text{LiAl}(\text{OBu}^t)_3\text{H}$ gave a Hammett plot that exhibited a ρ value of + 2.13. Reduction by a neutral $(\text{RO})_2\text{AlH}$ species, as had been suggested earlier²⁸ for $\text{LiAl}(\text{OBu}^t)_3\text{H}$, was excluded on the basis that the large ρ value suggested donation of the

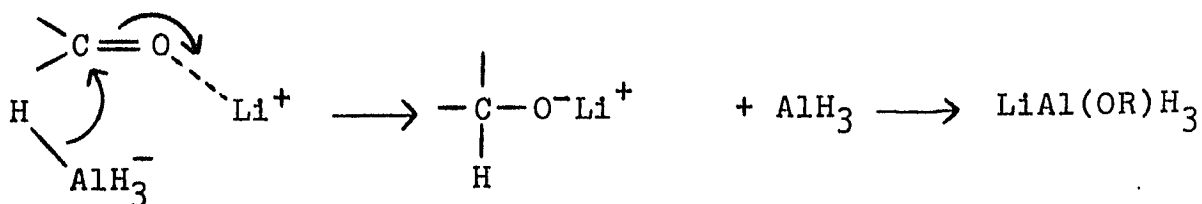
hydride by an anion such as $\text{Al}(\text{O}-\text{Bu}^t)_3\text{H}^-$.

The relative rates of reaction of a series of substituted benzophenones by aluminum hydride in THF has been reported.¹⁵ A ρ value of + 0.89 was obtained from a Hammett plot and interpreted that Lewis acid catalysis by AlH_3 is not significant in the reduction. It was concluded that the ketone must interact similarly in both transition states involving $\text{LiAl}(\text{OBU}^t)_3\text{H}$ and AlH_3 because the ρ value is positive in both cases. More importantly, it was reported that only one out of three to six hydrogen atoms of the AlH_3 solution was available for reduction of the benzophenones. The much slower rate of reaction of the second and third hydrogens of AlH_3 toward benzophenone is very surprising, since rapid reduction of alkyl ketones with the second and third hydrogens was observed.

The position of the transition state along the reaction coordinate for the reduction of a ketone by LiAlH_4 can only be speculative at this time. General arguments for early or late transition states for reduction of ketones by complex metal hydrides have been presented above. In addition results have been presented favoring a late transition state for LiAlH_4 reduction of cyclohexanones.²⁹ Stereochemical results from the reduction of 4-tert-butylcyclohexanone, 2-iso-propylcyclohexanone, and cis-4-tert-butyl-2-iso-propylcyclohexanone by LiAlH_4 at varying temperatures was used to calculate an A value of 1.7 kcal for the isopropyl group in 2-iso-propylcyclo-

hexanone in the transition state of the reaction. Since this value agrees closer to the value for the isopropyl group in cyclohexanes (1.7 kcal) than the value for 2-alkylcyclohexanones (0.4 kcal), it was concluded that the transition state was product-like.

A possible mechanism for reduction of ketones by LiAlH_4 has been suggested.³⁰ Based on Brown's and Lansbury's work demonstrating the importance of the lithium ion in borohydride reductions, it was suggested that prior or concurrent association of the carbonyl oxygen by Li^+ as the hydride is transferred from the aluminum to the carbon may be a mechanistic pathway for aluminohydride reduction. Recently experimental support for this mechanism was reported based on



the large amount of apparent equatorial attack on 2-methylcyclohexanone by $\text{Mg}(\text{AlH}_4)_2$ and ClMgAlH_4 . The observations³¹ were explained by complexation of the carbonyl oxygen by MgCl^+ or MgAlH_4^+ resulting in a change in the conformation of the ketone in the transition state.

Purpose

The purpose of this work was to determine the order behavior of LiAlH_4 and of AlH_3 in reaction with a ketone. The importance of the cation was investigated by comparing the rates of reaction of LiAlH_4 and NaAlH_4 . In order to try to determine if transfer of the hydride from aluminum to carbon is the rate determining step, a deuterium kinetic isotope study was conducted by comparing the rates of reaction of the ketone with LiAlH_4 and LiAlD_4 .

CHAPTER II

EXPERIMENTAL

Materials

LiAlH_4 and NaAlH_4 were obtained from the Ventron Corporation. Aluminum chloride (Fisher Scientific) was sublimed under nitrogen at 200–210°. Fisher reagent grade benzene and tetrahydrofuran (THF) were distilled under nitrogen from NaAlH_4 . Mesityl phenyl ketone was obtained by the reaction of benzoyl chloride with mesitylene. The product was distilled using a spinning band column (b.p. 113° at 0.30 mm; lit. 180–182° at 8.5 mm).³² GLC analysis of the distilled ketone showed it to be at least 99% pure. The nmr spectrum in CCl_4 using TMS as the reference showed the following signals: 7.6 δ , m, 5H; 6.85 δ , s, 2H; 2.29 δ , s, 3H; and 2.02 δ , s, 6H. Mass spectral analysis showed major peaks at 224 (M^+ , 91), 223 (100), 147 (58), 119 (15), 105 (17), and 77 (27), where the relative intensities are given in parentheses. U.V. and visible spectra in THF showed absorbance maxima at 348 m μ ($\epsilon = 93$) and 246 m μ ($\epsilon = 15,700$). Benzophenone and 2-methylbenzophenone were commercial samples purified by distillation.

Apparatus and Procedure

A Cary Model 14 recording spectrophotometer was used for recording visible and u.v. spectra over a number of wave lengths. A Zeiss PMQ II single-beam spectrophotometer was used for measuring absorbances at a single wave length. The cells used in this study were 10 mm quartz cells equipped with a two way teflon stopcock.

A F and M Model 700 flame ionization gas chromatograph equipped with a four foot glass column (10% Carbowax 20 M on Diatoport S) was used for glc analysis. Column temperature was 195-200°.

Calibrated syringes equipped with stainless steel needles were used for transfer of all reagents. All transfers were carried out under nitrogen in a glove box described elsewhere.³³

For kinetic studies with excess hydride, accurate volumes of standard hydride solutions were added to a known volume of THF in quartz cells with Hamilton 100, 250, and 500 ul syringes. The solutions were equilibrated at 25.0° in the cell compartment of the Zeiss PMQ II for fifteen minutes. Then a measured volume of a standard ketone solution was injected with a 100 ul syringe; the cell was shaken and the disappearance of the $\pi \rightarrow \pi^*$ band was followed at 246 m μ .

Preparations

Solutions of LiAlH_4 , LiAlD_4 and NaAlH_4 were prepared

by distilling THF from NaAlH_4 onto the hydride. The mixture was stirred overnight and filtered in the glove box using a fritted glass funnel and celite filter aid. The solutions were standardized by aluminum analysis (EDTA titration).

LiAlH_4 was recrystallized from a THF-benzene solvent mixture by repeated addition of benzene and partial removal of solvent under vacuum. The white solid was collected and dried under vacuum with continuous stirring to avoid any occlusion of benzene. A solution in THF was prepared from this LiAlH_4 as stated above. Analysis showed an Al:H:Cl ratio of 1.00:3.96:0.010. A solution of LiAlH_4 without any purification showed an Al:H:Cl ratio of 1.00:3.91:0.028.

NaAlH_4 was crystallized from a THF solution by the addition of benzene. The white solid was collected and dried under vacuum. A solution in THF was prepared from the recrystallized NaAlH_4 as stated above. Analysis showed a Li:Al:H:Cl ratio of 0.003:1.00:4.00:0.00.

The LiAlD_4 was used without further purification. Analysis showed an Al:H:Cl ratio of 1.00:3.90:trace.

A solution of aluminum hydride in THF was prepared by adding 3 moles of NaAlH_4 in THF to 1 mole of AlCl_3 in THF at -60° . The solution of AlCl_3 in THF was prepared by adding solid AlCl_3 to THF at -60° , allowing the solution to warm to 0° and then recooling to -60° before the NaAlH_4 was added. The reaction mixture was allowed to warm to 0° with stirring then re-cooled to -60° at which time the NaCl was allowed to

settle. A sample of the clear colorless solution was analyzed for sodium by flame spectrophotometry. If sodium was present an appropriate amount of AlCl_3 (as determined by the sodium analysis) was added at -60° . The solution was then allowed to warm to room temperature with stirring. The solution was filtered in the glove box using a fritted glass funnel and then stored in a freezer at -20° . Analysis of three preparations gave the following Na:Al:H:Cl ratios: 0.0018:1.00:2.93:0.0024; 0.0006:1.00:2.91:0.017, and 0.0009:1.00:2.97:0.016.

Solutions of mesityl phenyl ketone were prepared by dissolving a known amount of the ketone up to the mark in a volumetric flask equipped with a two-way stopcock. This solution was further diluted using a calibrated syringe and similar volumetric flasks. Reproducibility was better than $\pm 1.0\%$. Solutions of benzophenone and 2-methyl benzophenone were prepared similarly.

Ultraviolet and Visible Spectra

Tetrahydrofuran solutions of LiAlH_4 showed negligible absorbance down to 220 μ . Below 220 μ the solutions absorb strongly. Similarly the product solution from reaction of mesityl phenyl ketone with excess LiAlH_4 showed negligible absorbance in the 246 μ region. The extinction coefficient at 246 μ of the product was measured by reacting mesityl phenyl ketone (1.31×10^{-3} and $1.95 \times 10^{-3}\text{M}$) with excess LiAlH_4 .

(4.1×10^{-2} M). The results were values of 328 and 322 for the extinction coefficient. For the product the average value, $\epsilon = 325$, is only 2% of that for the starting ketone ($\epsilon = 15,700$).

A solution of mesityl phenyl ketone (5.38×10^{-5} M) and LiAlH_4 (1.04×10^{-2} M) was scanned in the 220-300 $\text{m}\mu$ region immediately after mixing. No shifts or changes in the $\pi \rightarrow \pi^*$ transition of the carbonyl group was observed except for its disappearing with time. Similarly the $n \rightarrow \pi^*$ transition (300-400 $\text{m}\mu$) was scanned for the reaction of ketone (7.75×10^{-3} M) and LiAlH_4 (2.02×10^{-2} M). Likewise no shifts or changes in $n \rightarrow \pi^*$ transition of the carbonyl group was observed except for its disappearing with time.

Product Analysis

Mesityl phenyl ketone (0.017 M) was allowed to react with LiAlH_4 (0.059 M) in THF. After 4 hours the reaction mixture was quenched with water and the THF removed under vacuum. Water was then added to the precipitate and the aqueous solution extracted three times with diethyl ether. The ether washings were combined and dried over MgSO_4 for fifteen minutes. The MgSO_4 was removed by filtration, the ether dried with Linde 4A Molecular Sieve and then the ether removed under vacuum. The nmr of the product in CCl_4 with TMS as the reference showed the following absorptions: 7.18 δ , s, 5H; 6.75 δ , s, 2H; 6.16 δ , s, 1H; 2.84 δ , s, 1H (concentration dependent); 2.22 δ , s, 3H;

and 2.12 δ , s, 6H which is in good agreement for the spectrum expected for mesitylphenylcarbinol. The reported³⁴ nmr spectrum for mesitylphenylcarbinol in CS₂ is 7.19 δ (phenyl); 6.69 δ (aromatic), 6.11 (methine), 2.20 δ (4-methyl), 2.11 δ (2,6-methyl), and 1.90 (hydroxyl). The product was a liquid although the literature reports³⁴ a melting point of 32°. The product remained a liquid even for a sample collected from a gas chromatograph. Mass spectral analysis showed major peaks at 226 (M⁺, 52), 208 (67), 193 (100), 149 (49), 147 (53), 121 (66), 105 (65), 79 (21), and 77 (36) where the relative intensities are given in parentheses.

In a similar reaction mesityl phenyl ketone (0.095 M) was allowed to react with LiAlD₄ (0.16 M) in THF. The reaction mixture was worked up as in the case of LiAlH₄. The nmr spectrum of the product in CCl₄ with TMS as reference showed the following absorptions: 7.18 δ , s, 5H; 6.75 δ , s, 2H; 3.32 δ (Concentration dependent), s, 1H; 2.22 δ , s, 3H; and 2.12, s, 6H which is in good agreement for the spectrum expected for mesitylphenylcarbinol with deuterium incorporation at the carbinol carbon atom. Mass spectral analysis showed peaks at 227 (M⁺, 42), 209 (67), 194 (100), 150 (44), 147 (44), 122 (38), 105 (69), 80 (17), and 77 (20) where the relative intensities are given in parentheses. Analysis of the mass spectrum for d₀, d₁, and d₂ species showed 4% d₀, 93% d₁, and 3% d₂.

The product of several reaction mixtures of mesityl

phenyl ketone with LiAlH_4 was analyzed by gas chromatography. Product analysis of reactions of 1.08×10^{-3} M ketone and 1.98×10^{-3} M LiAlH_4 , 1.31×10^{-3} M ketone and 4.08×10^{-2} M LiAlH_4 , 1.24×10^{-4} M ketone and 1.91×10^{-2} M LiAlH_4 , and 5.25×10^{-5} M ketone and 2.04×10^{-3} M LiAlH_4 showed only a single peak with the same retention time (30.5 minutes) as mesitylphenylcarbinol. The mesitylphenylcarbinol used here as a reference compound was prepared by reacting mesityl phenyl ketone with LiAlH_4 on a larger scale as described above and the product was shown to be mesitylphenylcarbinol by nmr and mass spectroscopy. A sample of this product from the reaction 5.22×10^{-5} M ketone and 1.01×10^{-2} M LiAlH_4 was collected from the gas chromatograph. Its mass spectral analysis also agreed with that of mesitylphenylcarbinol: 226 (M^+ , 55), 208 (42), 193 (100), 149 (50), 147 (49), 121 (50), 105 (92), 79 (27), and 77 (50) where the relative intensities are given in parentheses. Response ratios for mesityl phenyl ketone and the carbinol product were determined and the ketone used as internal standard since glc analysis had previously shown in each case that ketone was absent from the product mixture. Yields measured for several reactions were: 7.75×10^{-3} M ketone and 2.02×10^{-2} M LiAlH_4 , 98%; 1.08×10^{-3} M ketone and 1.98×10^{-3} M LiAlH_4 , 91%; 5.21×10^{-5} M ketone and 4.05×10^{-3} M LiAlH_4 , 93%; and 5.17×10^{-5} M ketone and 6.02×10^{-3} M LiAlH_4 , 97%.

Kinetic Experiments

Reaction rates were followed by observing the disappearance of the ketone band at 246 μ . Fifteen kinetic runs were carried out at constant ketone concentration (5×10^{-5} M) and a twenty-fold variation in LiAlH_4 (recrystallized) concentration (1×10^{-3} to 2×10^{-2} M). Six runs were made at constant LiAlH_4 concentration (1×10^{-2} M) and a twelve-fold variation in the ketone concentration (1×10^{-5} to 1.2×10^{-4} M).

Four kinetic runs were carried out using LiAlD_4 . Three reactions were carried out at constant ketone concentration (5×10^{-5} M) and a four-fold variation in LiAlD_4 concentration (5×10^{-3} to 2×10^{-2} M). Two runs were at constant LiAlD_4 concentration (1×10^{-2} M) and more than a two-fold variation in ketone (5×10^{-5} and 1.2×10^{-4} M).

Five kinetic runs were carried out using NaAlH_4 . Four were carried out at constant ketone concentration (5×10^{-5} M) and an eight-fold variation in NaAlH_4 concentration (5×10^{-3} to 4×10^{-2} M). Three runs were at constant NaAlH_4 concentration (1.9×10^{-2} M) and more than a two-fold variation in ketone (5×10^{-5} to 1.2×10^{-4} M) concentration.

Also seven kinetic runs were carried out using LiAlH_4 directly from the manufacturer. Five reactions were conducted at constant ketone concentration (5×10^{-5} M) and a ten-fold variation in LiAlH_4 concentration (4×10^{-3} to 4×10^{-2} M). Three runs were at constant LiAlH_4 concentration (1.5×10^{-2} M)

and a twelve-fold variation in ketone concentration (1×10^{-5} to 1.2×10^{-4} M).

Several kinetic runs similar to the above runs for LiAlH_4 using aluminum hydride and mesityl phenyl ketone were conducted. Aluminum hydride was also reacted with benzophenone and 2-methylbenzophenone in studies conducted to determine the number of reactive hydrogens in AlH_3 .

A plot of $\log (A - A_\infty)$ against time was made for each kinetic run. Each reaction was followed for two half lives (75% reaction) and an infinity reading was taken after the reaction stood overnight. The pseudo-first order rate constant (k_{obs}) was calculated from the slope of the line. The second order rate constant was calculated by dividing k_{obs} by the concentration of hydride.

CHAPTER III

RESULTS AND DISCUSSION

Mesityl phenyl ketone (MPK) reacts with excess lithium aluminum hydride in tetrahydrofuran (THF) to produce on hydrolysis the expected alcohol, mesitylphenylcarbinol, in high yield (95%) with no significant by-product formation.

Kinetics of Reduction of MPK by Lithium Aluminum Hydride

The reaction of MPK with excess LiAlH_4 was followed spectrophotometrically by observing the disappearance of the $\pi \rightarrow \pi^*$ transition of MPK at 246 μ ($\epsilon = 15,700$). Neither LiAlH_4 in THF nor the product ($\epsilon_{246} = 325$) solution absorbs significantly in this region when compared to MPK. In order to observe the transfer of only one of the hydrogens from LiAlH_4 to the ketone, the reaction was studied using LiAlH_4 in a twenty to four hundred molar excess. Using excess LiAlH_4 should avoid any significant reaction by any slower reacting alkoxy intermediate.

The ultraviolet region from 200 to 300 μ was scanned after initiating reaction. The maximum absorption band (carbonyl $\pi \rightarrow \pi^*$) remained at 246 μ with no changes detected except for disappearance of the 246 μ band with time. In a separate reaction the 300 to 450 μ region was scanned. The

maximum absorption band due to the $n \rightarrow \pi^*$ transition of the carbonyl group remained at 348 μ with no changes detected except for the disappearance of the 348 μ band with time. Thus, no band attributable to a complex between the carbonyl oxygen and lithium is observable in the ultraviolet or visible regions. This does not mean that a complex is not formed between the ketone and lithium since the concentration of the complex may be simply too small to detect or the complex band may be hidden under the free carbonyl band.

When MPK was added to excess LiAlH_4 , the absorbance at 246 μ disappeared in a first-order manner. Examples of several plots are given in Figure 1. Several runs were conducted at constant ketone concentration. The values for the pseudo-first-order rate constant (k_{obs}) are given in Table 1. A plot of k_{obs} vs. LiAlH_4 concentration gives a straight line passing through the origin (Figure 2) which is indicative of the reaction being first order in LiAlH_4 . If the reaction is first-order in ketone, k_{obs} should not change as the ketone concentration is varied at a constant LiAlH_4 concentration. This was found to be the case for a twelve-fold change in ketone concentration (see Runs 12-17, Table 1).

Conjugate addition of Grignard reagents to sterically hindered benzophenones is well known;³⁵ therefore, it was of concern that disappearance of the carbonyl could be taking place as a result of 1,4 and 1,6 addition as well as 1,2 addition. This possibility was checked by allowing MPK to react

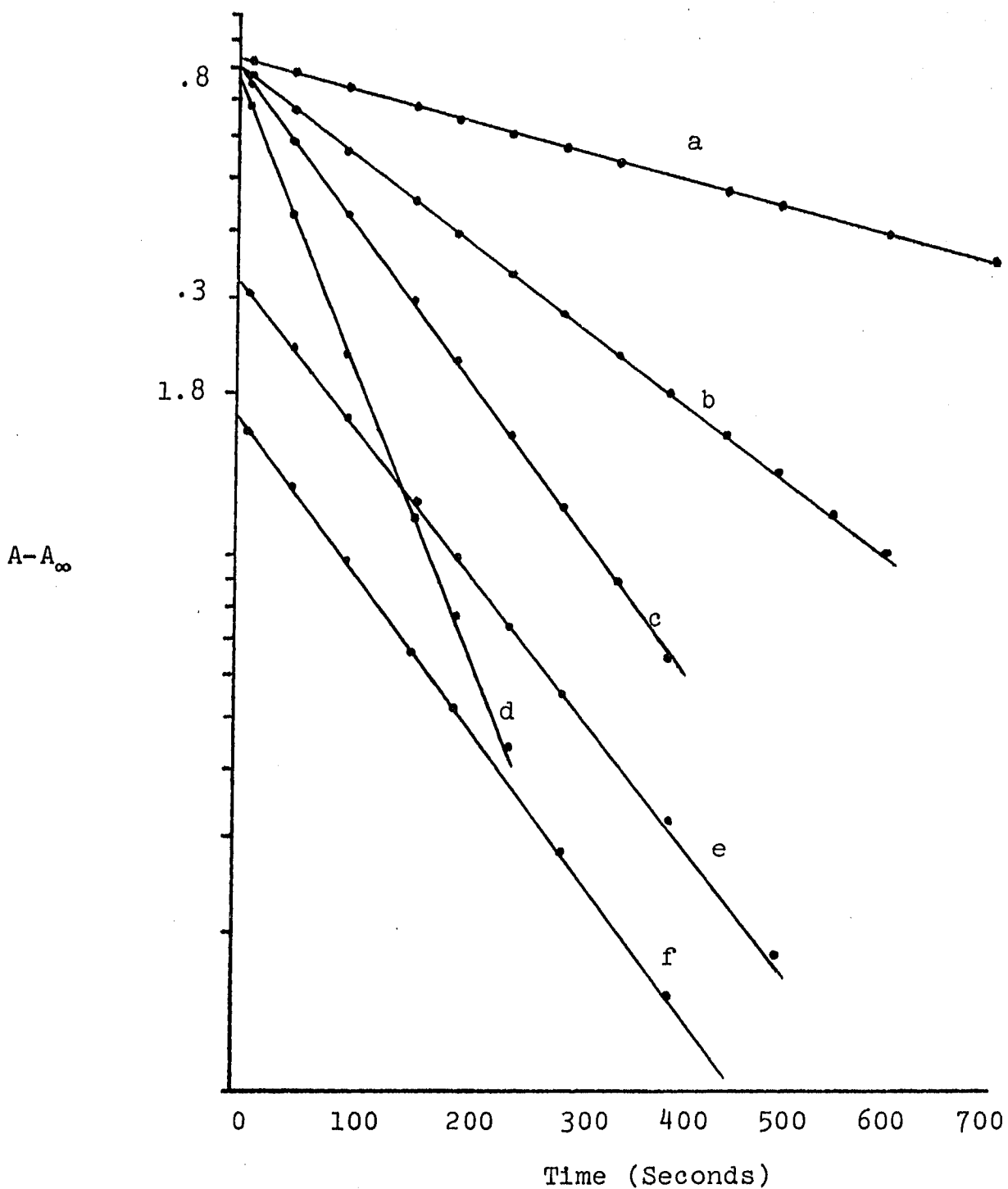


Figure 1. Reaction of Mesityl Phenyl Ketone with Excess LiAlH_4 . Concentrations are given in Table 1: (a) Run 3, (b) Run 7, (c) Run 14, (d) Run 20, (e) Run 13, (f) Run 17.

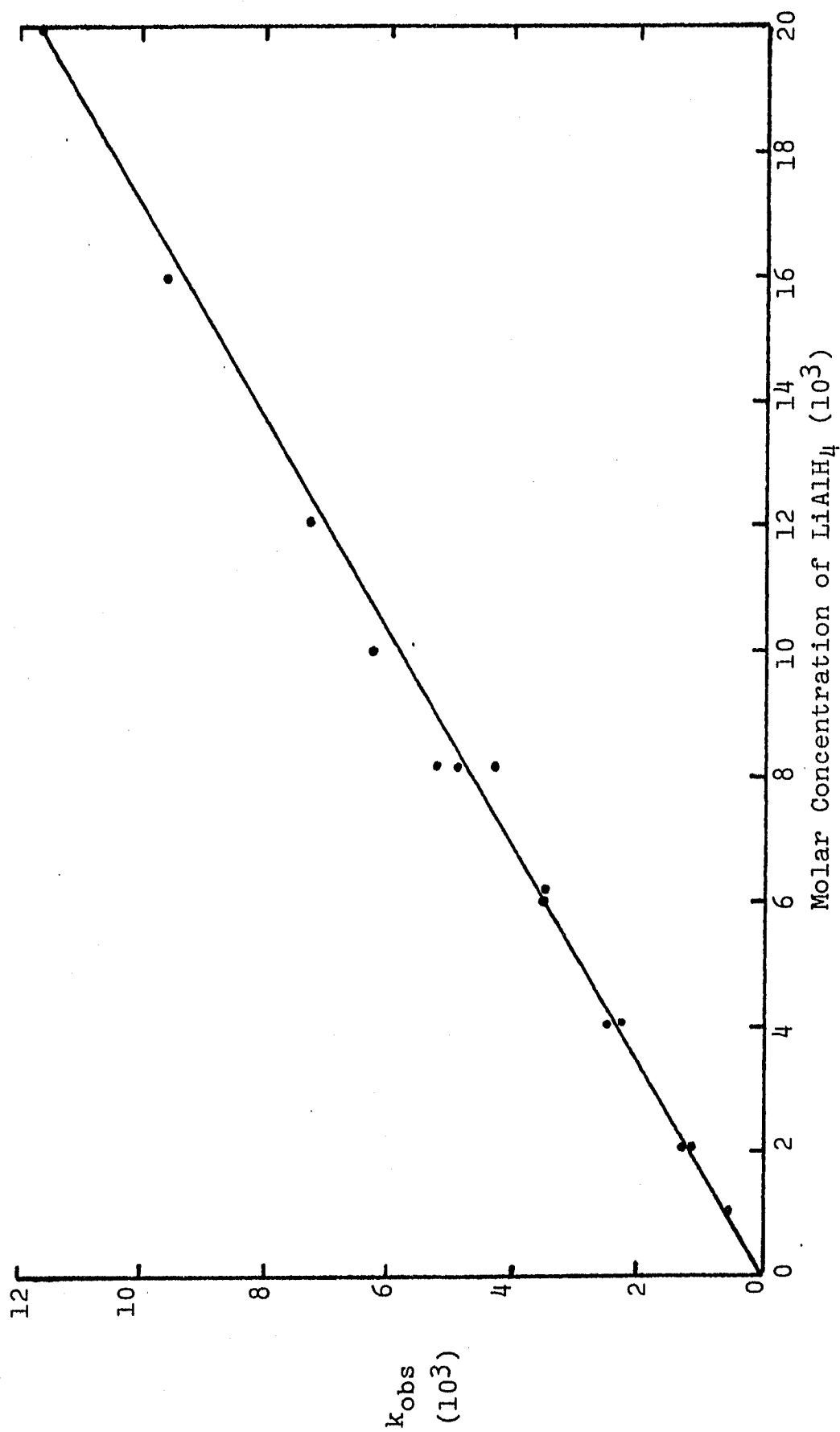
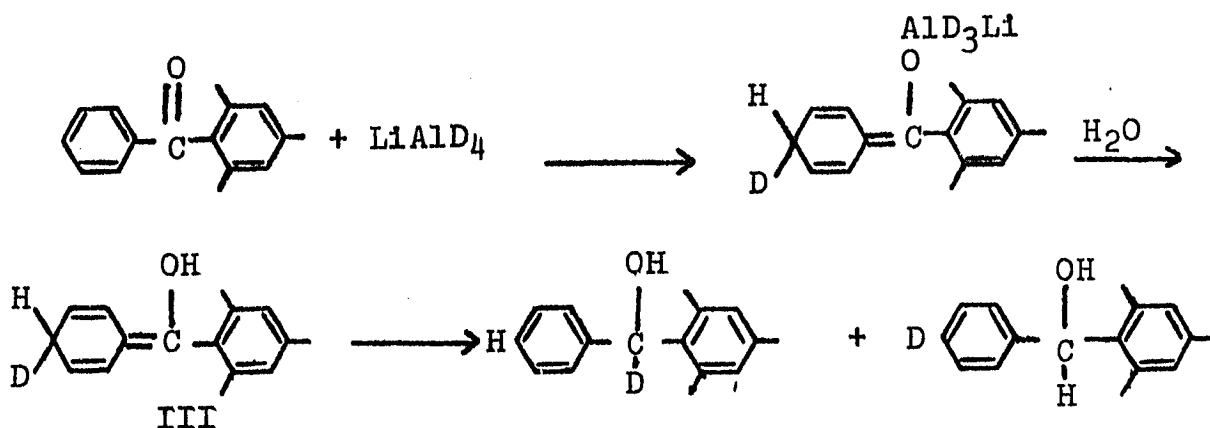


Figure 2. Reaction of 5.2×10^{-5} M Mesityl Phenyl Ketone with Varying Concentrations of LiAlH_4 . Data taken from Runs 1-11, 14, 18-20 of Table 1.

with LiAlD_4 . If 1-4 or 1-6 addition was occurring, then deuterium should be incorporated into the phenyl ring and hydrogen incorporated at the carbinol carbon since either the hydrogen or deuterium in III can migrate to form the products.



NMR analysis of the product of MPK and LiAlD_4 showed two absorptions for aromatic protons which integrated 5.0 to 2.0 and no absorption was observed for a hydrogen attached to the carbinol carbon atom. Thus it appears that reduction of MPK by LiAlH_4 takes place entirely in a 1,2 fashion.

GLC analysis of the product from reaction of MPK at 5.10^{-5} M with excess LiAlH_4 shows a single peak with the same retention time as mesitylphenylcarbinol. The mesitylphenylcarbinol used here as a reference was prepared by reacting mesityl phenyl ketone with LiAlH_4 on a larger scale as described in the experimental section and the product was shown to be mesitylphenylcarbinol by nmr and mass spectroscopy.

Analysis of the product by glc showed the ketone to be absent. The yields of several reactions were measured by using MPK as an internal standard and although not quantitative they were satisfactory. Reaction of 8×10^{-3} and 1×10^{-3} M MPK with approximately a two-fold molar excess of LiAlH_4 gave yields of 98 and 91%, respectively. Reaction of 5.2×10^{-5} M MPK with 4×10^{-3} and 6×10^{-3} M LiAlH_4 gave yields of 93 and 97%, respectively.

The second order rate constant (k_2) was calculated by dividing k_{obs} by the concentration of LiAlH_4 . The average value for runs 1-20 (Table 1) is $0.587 \text{ l mole}^{-1} \text{ sec}^{-1}$. The values obtained ranged from 0.522 to $0.641 \text{ l mole}^{-1} \text{ sec}^{-1}$. Very careful attention was given to runs 9, 10 and 11 which were run under identical conditions. The results indicate that the system is very sensitive; however, the low and high values of k_2 could not be related to one certain reaction cell giving high or low values, or to the concentration of LiAlH_4 , or whether the LiAlH_4 solution had been in the reaction cell for half an hour or a couple of hours before initiating the reaction. The low values for k_2 in runs 1 and 2 could be explained on the basis of hydrolysis of LiAlH_4 . The experience in this laboratory has been that manipulation of LiAlH_4 solutions in the concentration range 10^{-3} M and lower require somewhat elegant high vacuum techniques⁵ which were impossible to use to carry out these experiments. The spread ($\pm 10\%$) in the values of k_2 seems to be due to experimental

error since no pattern for k_2 variation could be established.

Reproducibility of runs 1-20 in Table 1 were checked against a second solution of LiAlH_4 (Table 2). The second solution of LiAlH_4 was prepared from unrecrystallized LiAlH_4 and from a different lot number. The two solutions gave average values for k_2 of 0.587 and 0.605 $\text{l mole}^{-1} \text{sec}^{-1}$, which are well within experimental error. This indicates, at least under pseudo-first-order conditions, that extreme purity of LiAlH_4 is not crucial. The second sample of LiAlH_4 was known from analysis to have more than twice the amount of chloride as the first (2.8% and 1.0% respectively). The chloride would probably be present either as LiAlH_3Cl which should react slower than LiAlH_4 or LiCl which should not react to any appreciable degree (complexation of carbonyl by Li^+ shown to be very weak). Therefore, the presence of LiAlH_3Cl or LiCl in such a large excess of LiAlH_4 should have a negligible effect on the reaction rate.

The reaction order of the reduction of MPK by LiAlH_4 as established in this study is second order, first order in ketone and first order in LiAlH_4 . Results are reproducible using different samples of LiAlH_4 .

Kinetics of Reduction of MPK by Sodium Aluminum Hydride

Several kinetic runs were carried out using NaAlH_4 under the same reaction conditions as used for LiAlH_4 . Just as in the case of LiAlH_4 , solutions of NaAlH_4 in THF did not

absorb significantly at 246 μ and thus the disappearance of the carbonyl group was followed as a measure of the rate of reaction. The band disappeared in a first-order fashion, (Figure 3), therefore the reaction is first-order in ketone. The values of k_{obs} and k_2 are given in Table 3. The average value of k_2 is $0.0526 \text{ mole}^{-1} \text{ sec}^{-1}$ over an eight-fold change in the concentration of NaAlH_4 . As with LiAlH_4 the results are not as reproducible as one would like. Even identical experiments (runs 30 and 31) showed a 16% variation in k_2 . However, the experimental error appears to be no greater than with LiAlH_4 and because of the extreme sensitivity of hydride solutions at 10^{-3} molar concentrations these results are probably about as reproducible as one might expect. In any event, it appears clear that the reaction is first-order in ketone and first-order in NaAlH_4 and that mesityl phenyl ketone reacts about eleven times faster with LiAlH_4 than with NaAlH_4 .

Obviously reaction of the aluminohydride ion with the ketone is not independent of the cation; if it were, equal rates of reaction of LiAlH_4 and NaAlH_4 would be expected. However, it is not entirely clear how the cation participates. The lithium cation could possibly enhance the reactivity of the ketone or the aluminohydride ion, or both.

Recent conductance studies⁵ carried out in this laboratory show that both are predominant ion pairs (> 85%) under the conditions of this kinetic study (25° and 1×10^{-3} to

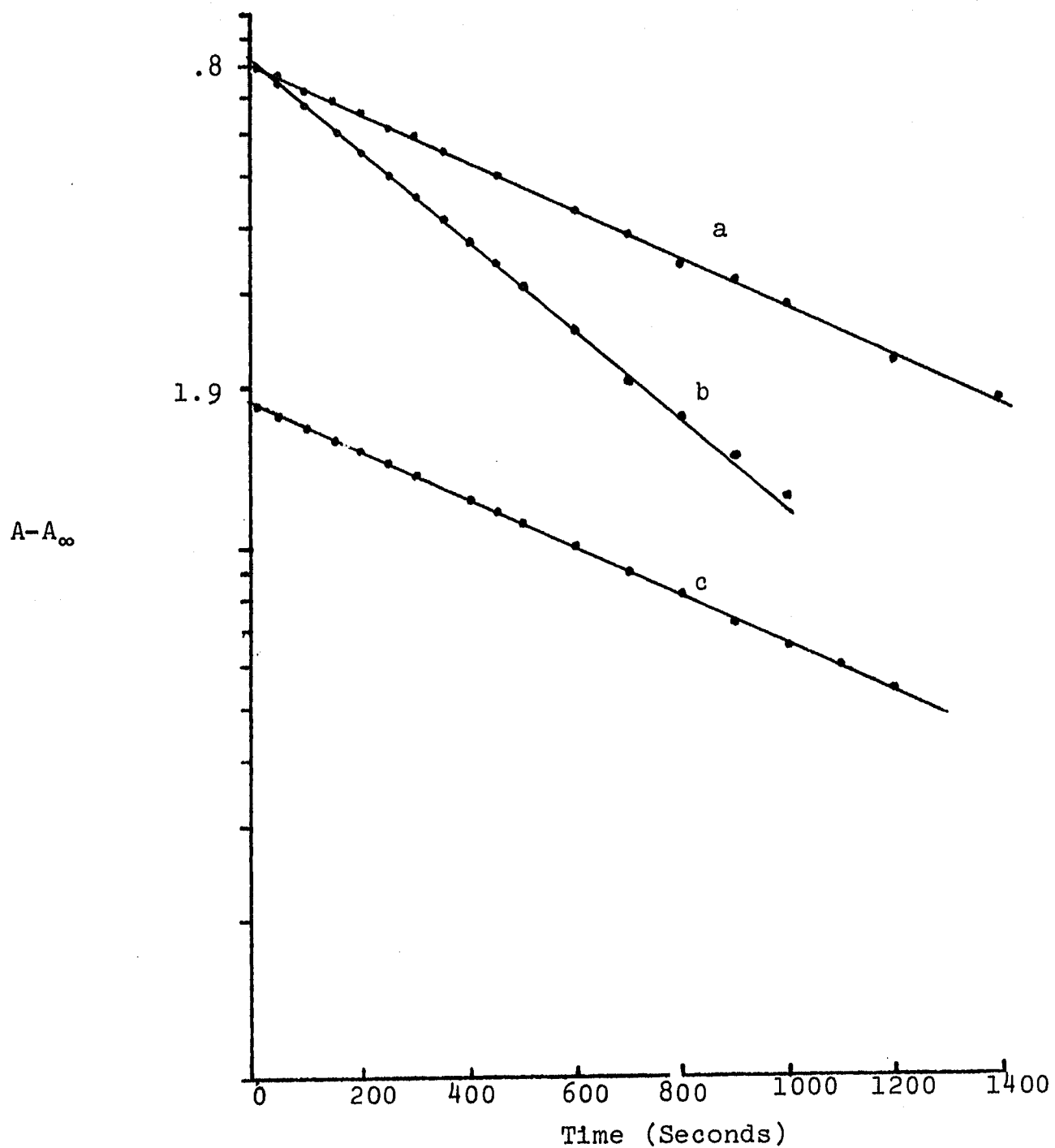
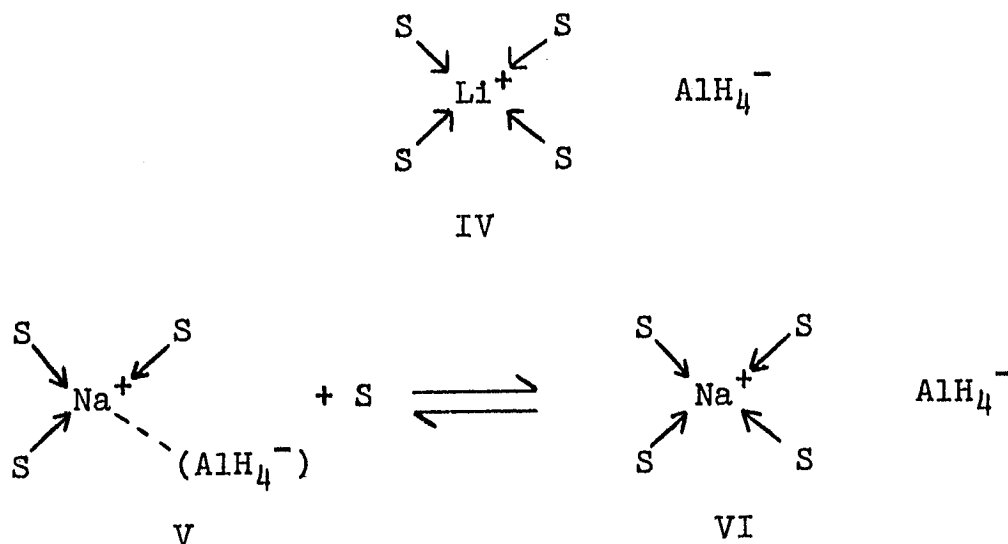


Figure 3. Reaction of Mesityl Phenyl Ketone with Excess NaAlH_4 . Concentrations are given in Table 3: (a) Run 30, (b) Run 32, (c) Run 29.

$4 \times 10^{-2} \text{ M}$). LiAlH_4 is a solvent separated ion pair under the conditions of the kinetic studies whereas NaAlH_4 appears to be a mixture of solvent separated and contact ion pairs.

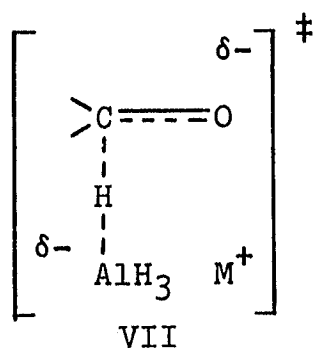


Approximately half the ion pairs of NaAlH_4 are solvent separated under the conditions of the kinetic studies. Also under the reaction conditions a small fraction of each hydride is present as free ions and triple ions.

Because the reaction rate of mesityl phenyl ketone with MAlH_4 depends upon the cation, M^+ , it seems reasonable to assume that the transition state involves an ion pair, M^+AlH_4^- , and not just the free aluminohydride ion.^{30,31} The fact that the stereoselectivity of MAlH_4 reductions are also dependent^{4,31} on the cation (M^+) suggests the presence of an ion pair (M^+AlH_4^-) in the transition state. Since both M^+ and AlH_4^- are present in the transition state and because the

ion pair is the major species in solution⁵ under the conditions of the kinetic experiments, it is reasonable to assume that the reactive species is the ion pair. Two possible mechanistic pathways for the reduction of mesityl phenyl ketone by MAlH_4 should be considered: (1) the cation does not complex the carbonyl oxygen and (2) the cation does complex the carbonyl oxygen. Since NaAlH_4 consists of both contact and solvent separated ion pairs in THF to about the same degree, reaction through both types of ion pairs needs to be considered. LiAlH_4 will be considered to react through the solvent separated ion pair, by far the most abundant species present in THF solution at ambient temperature.

The first mechanism suggested involves nucleophilic attack by the M^+AlH_4^- ion pair on the carbonyl carbon without the cation complexing the carbonyl oxygen. If one compares the solvent separated ion pair of NaAlH_4 (VI) to the



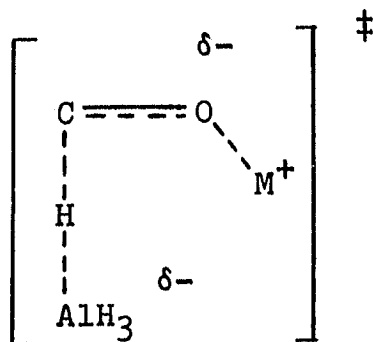
contact ion pair of NaAlH_4 (V), it might be expected that VI is the better nucleophile because the negative charge of the aluminohydride ion is less neutralized by the completely sol-

vated Na^+ compared to the partially solvated Na^+ . Since, VI should react faster than V and since V and VI are present in about equal amount, it appears likely that VI should be the major reactive species. If the reactive species is the solvent separated ion pair of LiAlH_4 (IV) and NaAlH_4 (VI), then NaAlH_4 and LiAlH_4 would be expected to have similar reaction rates according to transition state VII since the expected difference between completely solvated lithium and sodium ions should be small. However, LiAlH_4 is about eleven times more reactive towards MPK than NaAlH_4 , a difference that is not easily explained on the basis of the above mechanism involving transition state VII.

Perhaps the difference in the reaction rates of LiAlH_4 and NaAlH_4 (as depicted through transition state VII) could be better explained by LiAlH_4 reacting through IV and NaAlH_4 through V. The ion pair IV would be more reactive than V because as mentioned earlier, the partially solvated sodium ion in V neutralizes the charge of the aluminohydride ion more than the completely solvated lithium ion in IV. However, using the same reasoning, it was pointed out that probably VI and not V is the most reactive species for NaAlH_4 therefore to explain any rate differences in terms of IV and V does not seem reasonable. Clearly, transition state VII would appear more reasonable if the reaction rates of LiAlH_4 and NaAlH_4 towards MPK were more similar.

A second possible mechanism involves attack by the

$M^+AlH_4^-$ ion pair on the carbonyl group where the cation is bound to carbonyl oxygen during the reduction. This process



VIII

may simply involve the displacement of one molecule of THF solvent attached to M^+ by one molecule of ketone. In this case $LiAlH_4$ would be expected to react faster than $NaAlH_4$, either as the solvent separated or contact ion pair, since the smaller size of the lithium ion would allow it to associate more strongly with the carbonyl oxygen and to polarize the $C=O$ bond more than the sodium ion.

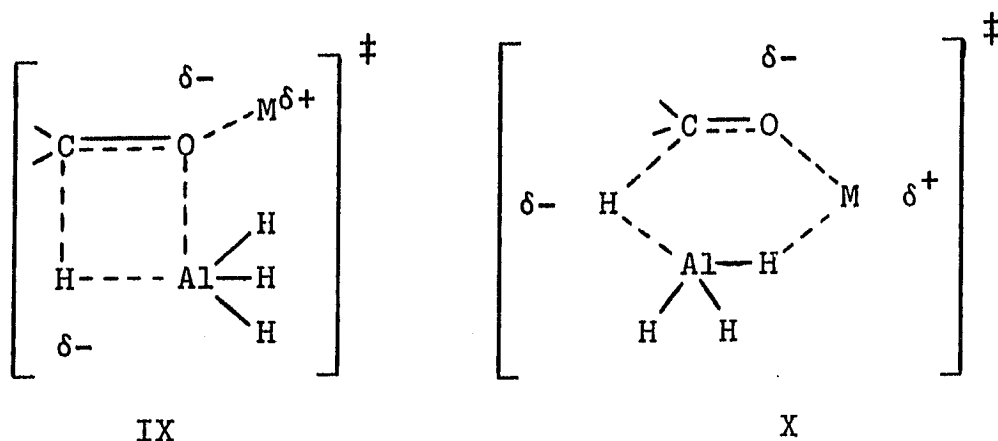
It has been shown⁵ that ketones associate with lithium ions in THF solutions of lithium salts. It is further known^{18,19} that $LiBH_4$ is more reactive than $NaBH_4$ towards ketones and esters. It is interesting that the difference in the reactivity between $NaBH_4$ and $LiBH_4$ have been explained on the basis of the difference in the electrophilic nature of the lithium and sodium ions.^{19,21,22} Thus, a transition state similar to VIII is more consistent than one like VII for $LiAlH_4$ reducing MPK at a faster rate than $NaAlH_4$.

Participation by the cation in the transition state is supported here not only by the difference in the reaction rates of LiAlH_4 and NaAlH_4 with MPK but also by the dependence of the cation on stereoselectivity of reduction of ketones by MAlH_4 compounds.^{4,31} The latter work also showed that the rate of reduction of camphor by NR_4AlH_4 (NR_4^+ = tri-n-ocetyl-n-propylammonium ion) is slower than by NaAlH_4 . Thus, the order of reactivity, $\text{LiAlH}_4 > \text{NaAlH}_4 > \text{NR}_4\text{AlH}_4$, is the same as the order of ability of the cation to associate with the carbonyl oxygen and polarize the $\text{C}=\text{O}$ bond (i.e., $\text{Li}^+ > \text{Na}^+ > \text{NR}_4^+$).

While polarization of the $\text{C}=\text{O}$ bond by M^+ gives an understandable explanation of rate differences between LiAlH_4 and NaAlH_4 , the effect of polarization or charge neutralization of the aluminohydride ion by M^+ on the reaction rate is more speculative. Transition state VII, as discussed above, would be better supported if equal rates of reaction of LiAlH_4 and NaAlH_4 with MPK were observed. In addition, if the reaction rate difference between LiAlH_4 and NaAlH_4 was explained on the basis that LiAlH_4 is a solvent separated ion pair (IV) and NaAlH_4 is a contact ion pair (V) as discussed for transition state VII, it would not be consistent with the fact that NR_4AlH_4 is less reactive than LiAlH_4 and NaAlH_4 . Although NR_4AlH_4 is a contact ion pair in solution, its center to center distance is greater than that of NaAlH_4 contact ion pair. Thus, NR_4^+ should neutralize the charge of the alumino-

hydride ion less than Na^+ and should be more reactive. This is not the case, NaAlH_4 is more reactive towards camphor than NR_4AlH_4 . It is believed that the best explanation for the order of reactivities of these aluminohydrides at present is the ability of the cation to complex and hence polarize the carbon oxygen bond of the ketone.

Structures VII and VIII are not drawn as detailed transition states and are intended only to reflect possible participation of the cation in the transition state. The association of the aluminum atom with the carbonyl oxygen (IX) or M-H-Al bridging (X) may or may not occur in the transition state. These are real possibilities and cannot be distinguished from VII and VIII by kinetic data.



It has been assumed that the reactive species is the ion pair, M^+AlH_4^- , because both M^+ and AlH_4^- are present in the transition state. If the ion pair is the attacking species, the attack by M^+ on the carbonyl oxygen may be prior to or

synchronous with a rate determining hydride transfer step. Another possibility may be that the attacking species is not the ion pair $M^+AlH_4^-$ but free ions where the carbonyl group associates with a free M^+ and then is attacked by a free AlH_4^- . In this connection, from the report of Dobbs⁵ that $LiAlH_4$ and $NaAlH_4$ have approximately the same amount of free ions in solution and because $LiAlH_4$ reacts approximately 10 times faster than $NaAlH_4$, it appears more reasonable that solvent separated ion pairs are involved.

Kinetics of Reduction of MPK by Lithium Aluminum Deuteride

Four kinetic experiments were carried out using excess $LiAlD_4$ to reduce MPK. The values of k_{obs} and k_2 are given in Table 4. The disappearance of the $\pi \rightarrow \pi^*$ band was first order in the case of $LiAlD_4$ as was observed for $LiAlH_4$. The value of k_2 is independent of the $LiAlD_4$ concentrations (runs 33, 34, and 36) and the ratio of ketone to $LiAlD_4$ (runs 34 and 35) within experimental error.

The average value of k_2 obtained using $LiAlD_4$ was $0.461 \text{ mole}^{-1} \text{ sec}^{-1}$. The value of k_H/k_D is 1.27 ± 0.14 . Interpretation of k_H/k_D is not straight forward because it represents both primary and secondary deuterium isotope effects.

Sodium borohydride reduction of ketones as well as aqueous hydrolysis of $NaBH_4$ gives a k_H/k_D value of about 0.7.^{7,25,36} The inverse isotope effect for hydrolysis was thought to consist^{36,37} of two parts: (1) a small normal

primary kinetic isotope effect arising from the B-H bond breaking in the rate determining step, and (2) an inverse secondary kinetic isotope effect arising from the stiffening of the B-H bonds not breaking in the rate determining step. The inverse secondary effects were said to mask the primary effect. The secondary B-H bonds in the transition state were assumed to resemble those of borane. The B-H bonds of borane have higher vibrational frequencies than those of the borohydride ion, thus the explanation that the secondary B-H bonds stiffen in the transition state. The alcoholysis of LiAlH_4 gave a $k_{\text{H}}/k_{\text{D}} = 0.93$ and 0.99 at -78° and -25° , respectively, and NaBH_4 gave a $k_{\text{H}}/k_{\text{D}} = 0.53$ and 0.63 at the same temperatures. The smaller isotope effect for LiAlH_4 compared to NaBH_4 was explained on the basis of less bond stiffening for the Al-H bonds than the B-H bonds in the transition state. The difference in vibrational frequencies between LiAlH_4 (1724 cm^{-1}) and AlH_3 (1778 cm^{-1}) are less than NaBH_4 (2264 cm^{-1}) and BH_3 (2560 cm^{-1}).

It is reasonable that the reduction of ketones by sodium borohydride gives an inverse isotope effect³⁶ because the secondary isotope effect masks the small primary isotope effect. If the secondary isotope effects for NaBH_4 and LiAlH_4 are inverse, but smaller for LiAlH_4 than NaBH_4 , then the small value of $k_{\text{H}}/k_{\text{D}}$ reported here for LiAlH_4 may be explained by a small primary isotope effect which is not completely masked by secondary effects. The small isotope effect would then be

consistent with a rate determining step involving transfer of the hydride from the aluminum to the carbonyl carbon. The small value of k_H/k_D is consistent with both an early or late transition state. However, the interpretation of the magnitude of the isotope effect is not clear not only because of the secondary isotope effect, but also because of the uncertainty of the Al...H...C angle in the transition state, and other possible factors.⁷ In recent years an increasing number of theories and examples have been presented contrary to the concept of product development control, which supposedly requires a late transition state. Although the small k_H/k_D value presented is not proof for an early transition state, it is not inconsistent with this concept.

Kinetics of Reduction of MPK by Aluminum Hydride

Preparation of aluminum hydride by adding 100% H_2SO_4 to THF solutions of $LiAlH_4$ ³⁸ and $NaAlH_4$ was not successful. The resulting AlH_3 solution produced solutions of AlH_3 containing 5-15% (based on aluminum) alkali metal ion in solution. The aluminum hydride was best prepared by adding 3 moles of $NaAlH_4$ to 1 mole $AlCl_3$ in THF. The sodium analysis was less than 0.2% of the aluminum analysis.

It had been reported¹⁵ that only one-third of the total hydrogen in a tetrahydrofuran solution of aluminum hydride is available for reduction of benzophenone. This was rather surprising since we had shown earlier that di-tert-

butoxyaluminumhydride reduces ketones.⁴ It was felt that the report claiming the lack of reactivity of the last two hydrogen atoms on AlH_3 should be checked. Reaction of benzophenone with an excess of AlH_3 , after 3 hours, gave only benzhydrol as a product with no recovered ketone. The yield was 95% measure by glc analysis using an internal standard (benzophenone). When the reaction was run at a ratio of 3 moles of benzophenone to 1 mole AlH_3 the relative yield of benzohydrol was 76% after 4 hours and 81% after 1 day. Similar yields were obtained for 2-methylbenzophenone after 1 day reaction time. When 2 moles of 2-methylbenzophenone were allowed to react with 1 mole of AlH_3 and the reaction followed spectrophotometrically, the $n \rightarrow \pi^*$ band at 346 $\text{m}\mu$ showed an 80% decrease in absorbance after 2 hours. These results demonstrate that the second hydrogen, and to some extent the third hydrogen, is capable of reducing benzophenone.

Pseudo-first order kinetics using excess AlH_3 and PMK did not prove to be successful. Results are given in Table 5. Although the disappearance of the $\pi \rightarrow \pi^*$ band at 246 $\text{m}\mu$ did follow a first-order disappearance, the values of k_{obs} and k_2 are very inconsistent. The values of k_{obs} did not increase linearly as the concentration of AlH_3 was increased at constant ketone concentration (runs 37-43 and 52) and instead were sporadic. As a result of the sporadic behavior of k_{obs} the values of k_2 ($k_{\text{obs}}/[\text{AlH}_3]$) varied over a seven-fold

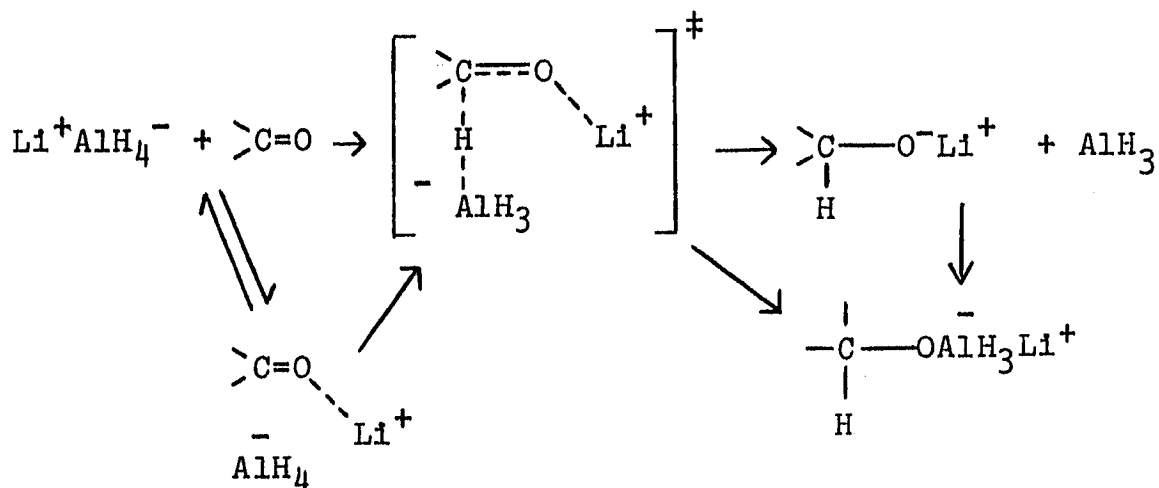
range. At constant hydride concentration and varying the ketone concentration, k_{obs} varied over more than a two-fold range (runs 44-51). The variations in k_{obs} and k_2 (assuming first-order behavior in AlH_3) did not follow any definite pattern as the ratio of AlH_3 :ketone decreased. GLC analysis of the product showed only a single peak corresponding to mesitylphenylcarbinol.

The inconsistency of these results were very disappointing and made interpretation of the results highly questionable. It was believed initially that the AlH_3 system would be simpler than LiAlH_4 and easier to interpret since LiAlH_4 presents the possibility of three species in the transition state, the Li^+ ion, the AlH_4^- ion and the ketone, whereas AlH_3 involves only two species, namely, AlH_3 and ketone. The only information that could possibly be extracted from Table 5 is that AlH_3 is about ten times less reactive towards MPK than LiAlH_4 .

Conclusions

The reaction of LiAlH_4 with MPK under the conditions of this study is first-order in LiAlH_4 and first-order in MPK. The deuterium kinetic isotopic effect, $k_{\text{H}}/k_{\text{D}} = 1.27 \pm 0.14$, indicates that rate controlling step is the transfer of the hydride from the aluminum to the carbonyl carbon. The difference in reactivities between NaAlH_4 and LiAlH_4 indicates that the transition state evolves the ion pair M^+AlH_4^- . The greater

reactivity of LiAlH_4 compared to NaAlH_4 may be explained by coordination of lithium with the carbonyl oxygen, thus assisting in the hydride transfer. The following mechanism would be consistent with the reported results.



This work shows that LiAlH_4 reduction of suitable ketones occur at rates which can be measured. Further work should involve: the determination of thermodynamic parameters (E_a , ΔS^\ddagger , etc), kinetic studies at lower reactant ratios, investigations of the roll of alkoxy intermediates, and further investigations of the participation of the cation in the reduction.

Results with aluminum hydride and MPK were not very conclusive. Aluminum hydride was found to be about ten times less reactive towards MPK than LiAlH_4 .

Table 1. Reaction of LiAlH_4 with Mesityl Phenyl Ketone in THF at 25.0° .

Run	Conc. LiAlH_4 $\underline{\text{M}} \times 10^3$	Conc. MPK $\underline{\text{M}} \times 10^5$	$k_{\text{obs}} \times 10^3$ (sec^{-1})	k_2 (1 mole $^{-1}$ sec^{-1})
1	1.02	5.27	0.530	0.528
2	1.02	5.27	0.534	0.524
3	2.04	5.25	1.24	0.607
4	2.04	5.25	1.13	0.552
5	4.05	5.21	2.22	0.549
6	4.05	5.21	2.49	0.616
7	6.02	5.17	3.50	0.582
8	6.19	5.31	3.50	0.566
9	8.19	5.27	4.28	0.522
10	8.19	5.27	4.88	0.596
11	8.19	5.27	5.25	0.641
12	9.93	1.02	5.98	0.602
13	10.2	2.10	5.98	0.589
14	10.1	5.22	6.24	0.618
15	10.1	8.32	6.36	0.629
16	10.1	10.4	6.24	0.618
17	10.1	12.4	6.18	0.613
18	12.1	5.18	7.30	0.603
19	16.0	5.24	9.63	0.602
20	20.0	5.15	11.7	0.587

Table 2. Reaction of LiAlH_4^a with Mesityl Phenyl Ketone in THF at 25.0° .

Run	Conc. LiAlH_4 $\underline{M} \times 10^3$	Conc. MPK $\underline{M} \times 10^5$	$k_{\text{obs}} \times 10^3$ (sec^{-1})	k_2 (1 mole $^{-1}$ sec $^{-1}$)
21	4.68	5.21	2.77	0.591
22	7.74	5.19	5.10	0.659
23	15.1	1.02	9.25	0.612
24	15.1	5.06	9.50	0.628
25	14.9	12.0	9.25	0.620
26	30.2	5.04	16.9	0.560
27	45.1	5.04	25.6	0.568

^aNot recrystallized.

Table 3. Reaction of NaAlH_4 with Mesityl Phenyl Ketone in THF at 25.0° .

Run	Conc. NaAlH_4 $\text{M} \times 10^3$	Conc. MPK $\text{M} \times 10^5$	$k_{\text{obs}} \times 10^3$ (sec^{-1})	$k_2 \times 10$ (1 $\text{mole}^{-1} \text{sec}^{-1}$)
28	5.34	5.25	0.284	0.532
29	18.7	12.4	1.06	0.567
30	18.9	5.21	1.06	0.561
31	18.9	5.21	0.905	0.479
32	40.4	5.24	1.98	0.490

Table 4. Reaction of LiAlD_4 with Mesityl Phenyl Ketone in THF at 25.0° .

Run	Conc. LiAlD_4 $\text{M} \times 10^3$	Conc. MPK $\text{M} \times 10^5$	$k_{\text{obs}} \times 10^3$ (sec^{-1})	k_2 (1 mole $^{-1}$ sec^{-1})
33	5.07	5.13	2.40	0.473
34	9.86	12.5	4.58	0.460
35	9.95	5.25	4.59	0.466
36	19.7	5.21	8.72	0.443

Table 5. Reaction of AlH_3 with Mesityl Phenyl Ketone in THF at 25.0° .

Run	Conc. AlH_3 $\underline{\text{M}} \times 10^3$	Conc. MPK $\underline{\text{M}} \times 10^5$	$k_{\text{obs}} \times 10^3$ (sec^{-1})	$k_2 \times 10^2$ (1 $\text{mole}^{-1} \text{sec}^{-1}$)
37	4.58	5.15	0.0714	1.56
38	7.72	5.20	0.834	10.8
39	14.2	4.80	0.608	4.29
40	22.4	5.12	0.532	2.38
41	23.8	4.80	1.69	7.13
42	28.7	5.16	1.26	4.39
43	47.4	4.80	2.77	5.85
44	95.3	0.965	4.78	5.01
45	95.2	1.06	3.16	3.32
46	95.1	2.90	4.00	4.28
47	95.0	3.18	3.75	3.95
48	94.7	6.32	3.65	3.85
49	94.5	8.60	3.68	3.90
50	94.1	11.6	3.28	3.23
51	93.9	12.5	1.85	1.97
52	190	4.69	9.00	4.73

LITERATURE CITED*

1. J. Klein, Tetrahedron Lett., 4307 (1973); and references therein.
2. N. T. Anh, O. Eisenstein, J.-M. Lefour and M. E. Tran Huu Dau, J. Amer. Chem. Soc., 95, 6146 (1973).
3. E. L. Eliel and Y. Senda, Tetrahedron, 26, 2411 (1970), and references therein.
4. Unpublished studies by E.C. Ashby, R. Boone, J. Gamble and J. Sevenaire (1960-73).
5. E. C. Ashby, Frank R. Dobbs and Harry P. Hopkins, J. Amer. Chem. Soc., 95, 2823 (1973); and unpublished results.
6. T. E. Hogen-Esch and J. Smid, J. Amer. Chem. Soc., 88, 318 (1966).
7. D. C. Wigfield and D. J. Phelps, Can. J. Chem., 50, 388 (1972) and references therein.
8. P. Geneste, G. Lamaty, C. Moreau and J. P. Roque, Tetrahedron Lett., 5011 (1970) and references therein.
9. K. Bowden and M. Hardy, Tetrahedron, 22, 1169 (1966).
10. J. A. Perry and K. D. Warren, J. Chem. Soc., 4049 (1965).
11. G. G. Smith and R. P. Bayer, Tetrahedron, 18, 323 (1962).
12. H. C. Brown and K. Ichikawa, J. Amer. Chem. Soc., 83, 4372 (1961).
13. H. C. Brown, O. H. Wheeler and K. Ichikawa, Tetrahedron, 1, 214 (1957).
14. E. R. Garrett and D. A. Lyttle, J. Amer. Chem. Soc., 75, 6051 (1953).
15. D. C. Ayers, D. N. Kirk and R. Sawdaye, J. Amer. Chem. Soc., B, 1133 (1970).

*For the complete titles of all journals referred to, see Access, 1969.

16. J. Klein, E. Dunkelblum, E. L. Eliel and Y. Senda, Tetrahedron Lett., 6127 (1968).
17. H. C. Brown, E. J. Mead and C. J. Shoaf, J. Amer. Chem. Soc., 78, 3616 (1956).
18. H. C. Brown, E. J. Mead and B. C. Subba Roa, J. Amer. Chem. Soc., 77, 6209 (1955).
19. H. C. Brown and K. Ichikawa, J. Amer. Chem. Soc., 83, 4372 (1961).
20. P. Geneste and G. Lamaty, Bull. Soc. Chim. Fr., 669 (1968).
21. P. T. Lansbury, R. E. MacLeay and J. O. Peterson, Tetrahedron Lett., 311 (1964).
22. P. T. Lansbury and R. E. MacLeay, J. Amer. Chem. Soc., 87, 831 (1965).
23. H. C. Brown and I. Ichikawa, Tetrahedron, 1, 221 (1957).
24. P. Geneste, G. Lamaty, and J. P. Roque, Tetrahedron Lett., 5007 (1970).
25. D. C. Wigfield and D. J. Phelps, Chem. Commun., 1152 (1970).
26. H. C. Brown and R. F. McFarlin, J. Amer. Chem. Soc., 80, 5372 (1958).
27. H. Haubenstock and E. L. Eliel, J. Amer. Chem. Soc., 84, 2363 (1962).
28. H. C. Brown and H. R. Deck, J. Amer. Chem. Soc., 87, 5620 (1965).
29. H. M. Cense, Tetrahedron Lett., 2153 (1972).
30. H. O. House, "Modern Synthetic Organic Reactions," W. A. Benjamin, Inc., New York, 1972, p. 49.
31. E. C. Ashby, J. R. Boone and J. P. Oliver, J. Amer. Chem. Soc., 95, 5427 (1973).
32. A. M. DeRoos, Recl. Trav. Chim. Pays. Bas., 87, 1359 (1968).
33. T. L. Brown, D. W. Dickerhoof, D. A. Bufus, and G. L. Morgan, Rev. Sci. Instr., 33, 491 (1962).

34. A. Mannschreck and L. Ernst, Chem. Ber., 104, 228 (1971).
35. T. Holm and I. Crossland, Acta. Chem. Scand., 25, 59 (1971).
36. R. E. Davis, R. E. Kenson, C. L. Kibby, and H. H. Lloyd, Chem. Commun., 593 (1965).
37. R. E. Davis, E. Bromels and C. L. Kibby, J. Amer. Chem. Soc., 84, 885 (1962).
38. H. C. Brown and N. M. Yoon, J. Amer. Chem. Soc., 88, 1464 (1966).

VITA

James R. Boone was born November 10, 1946, in Brownsville, Tennessee. He was reared in Alamo, Crockett County, Tennessee. After graduating from Alamo High School in 1964, he entered Freed Hardeman College, Henderson, Tennessee and received an A. A. degree in 1966. He received his B. A. degree from David Lipscomb College, Nashville, Tennessee in 1968.

In September, 1968, James entered graduate school at Georgia Tech in the School of Chemistry on a NDEA Fellowship. He began his research under the direction of Dr. E. C. Ashby in January, 1971.

He is married to the former Rosemary Bramlette of Atlanta, Georgia.